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## INDEX NUMBER


JUNE 1952

VOLUME 65 NUMBER 6

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Oct. 30, 1917, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00


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# Luzier's Service In The Field Of Allergy

When patient has history of cosmetic sensitivity, or when cosmetics may reasonably be suspected as a contributing if not the etiological factor in your patient's symptoms of allergy, we suggest:

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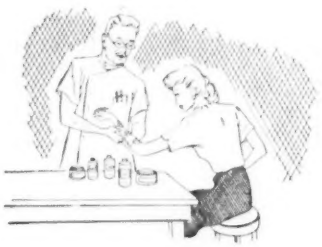

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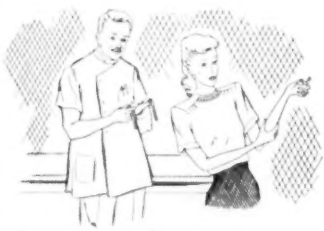
3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)



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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

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7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.


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*Harrison, T. R.: *Principles of Internal Medicine*, Philadelphia, The Blakiston Company, 1950, p. 981

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*For your information the Chemical Division of The Procter & Gamble Company has prepared this article, discussing some of the differences between synthetics and soaps which formerly were widely used for household washing.*

## How synthetic detergents differ from soaps

Synthetic detergents are organic compounds with molecules whose opposite ends are highly polarized like those of soap; one end consists of the type of structure which is oil soluble, the other consists of the type which is water soluble.

Magnesium and calcium soaps formed by interaction of sodium soaps with water hardness are among the most insoluble of compounds. The precipitation which occurs with soap in hard water wastes soap and causes cloudy glassware and unsightly deposits. The "tailor-made" molecules of synthetics do not form these insoluble compounds in hard water. They, therefore, leave surfaces cleaner because they are free of any precipitated "soap film" formed during rinsing. Also, unlike soaps, in solution, synthetics can be used at almost any pH. Soaps, of course, must be kept at pH 10 or above, or they will split into fatty acids. Most synthetic products in general use have solution pHs from 6.0—10.0. Few are above the pH of soap.

## The special washing abilities of synthetic detergents

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## The effect of synthetic detergents on bacteria

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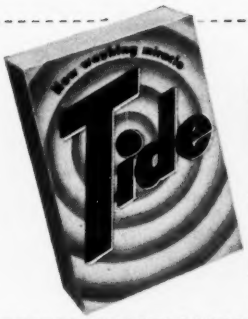


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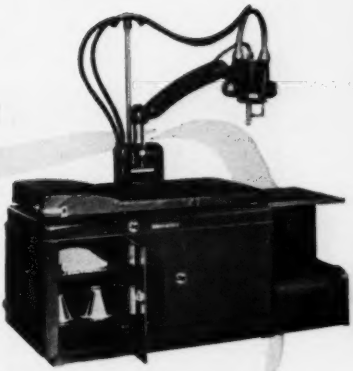

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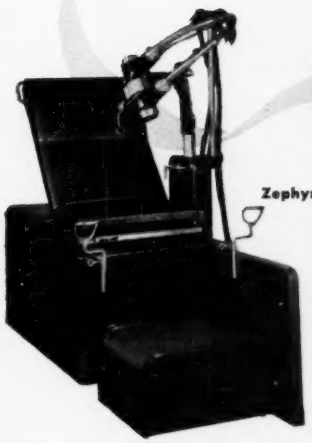

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Ehrlich, N. J., and Kaplan, M. A. (1950)
Ann. Allergy, 8:682, Sept.-Oct.

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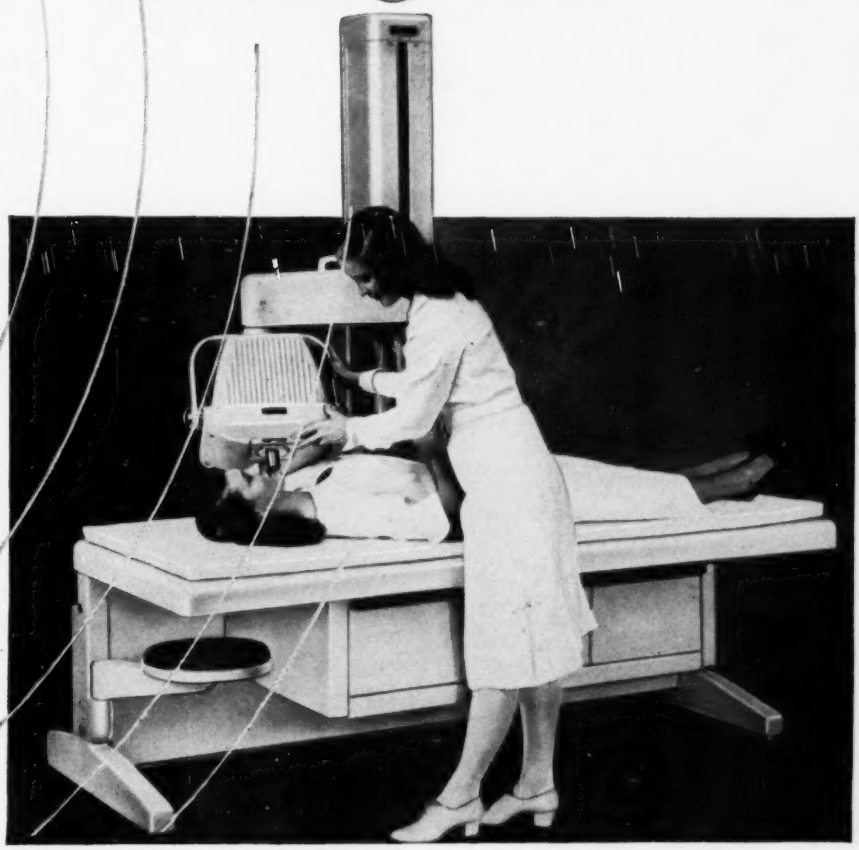

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# DO ROENTGEN-RAY TREATMENTS AS GIVEN BY SKIN SPECIALISTS PRODUCE CANCERS OR OTHER SEQUELAE?

## Follow-Up Study of Dermatologic Patients Treated with Low-Voltage Roentgen Rays

MARION B. SULZBERGER, M.D.
RUDOLF L. BAER, M.D.
AND
ALEXANDER BOROTA, M.D.
NEW YORK

THIS REPORT deals with systematic follow-up and examination of the skin of persons who 5 to 23 years previously had received superficial low-voltage roentgen-ray treatments. The examinations were carried out by qualified specialists in dermatology in order to ascertain what, if any, harmful sequelae or other visible late effects had occurred.

The term superficial low-voltage roentgen-ray treatment is here used to designate the quality and dosage almost universally employed by skin specialists in hospitals, clinics, and private offices in the United States. In most dermatoses, the customary practice is to administer to any one area no more than 85 r weekly or 42.5 r once to twice weekly, up to a maximum total dose of about 1,400 r. These figures are based on dosages measured in air. The usual quality of irradiation used ranges from 60 to 100 kv., with half-value layers of about 0.5 to 1 mm. Al; only in exceptional cases will the voltage used go as high as 120 kv., with half-value layers up to 3 mm. Al. For many years this quality and dosage of low-voltage roentgen-ray treatment have been used by dermatologists in the therapy of a great variety of entirely nonmalignant, nondangerous, benign skin conditions—among them acne vulgaris, "eczema," psoriasis, "neurodermatitis," and severe and "intractable" itching of diverse areas.

After more than 30 years of experience, the large majority of qualified skin specialists in the United States feel certain that the use of superficial roentgen-ray treatments in the described fractional doses and within the stated limits of maximum dosage is not merely safe and justifiable but is, as a matter of fact, among the best therapeutic measures in selected cases of many benign dermatoses. For it is the recorded dermatologic experience that such treatments "cure" or materially benefit

Dr. H. M. C. Luykx and Dr. D. Mainland helped in statistical matters. Miss Santa Forgione gave technical assistance.

Read before the Seventy-first Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., May 26, 1951.

This study was made possible by grants from the Biological Sciences Division of the Office of Naval Research and the United States Atomic Energy Commission.

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many patients with skin eruptions which fail to respond to other accepted forms of treatment, thus lessening the periods of disability and often also the risks of permanent physical or psychological damage that would otherwise result from the dermatosis.

Acne vulgaris, for example, is one of the commonest and most disfiguring among the many dermatoses which frequently respond to superficial roentgen rays. The question is often asked whether it is justifiable to administer superficial roentgen-ray treatments in cases of acne vulgaris, which is not only a benign but usually also a self-limited dermatosis. But acne vulgaris is not a negligible disease. It is in fact the most frequent cause of disfigurement among adolescents and young adults and often brings about irremediable emotional maladjustments and lifelong psychic scarring, in addition to the cutaneous scarring of the face and other areas. For these reasons, experienced skin specialists who know the disease best are in general agreement that superficial roentgen-ray treatments are not only justifiable in many cases of acne vulgaris but are indeed mandatory, particularly when other forms of therapy have failed.

In contrast to this almost universal opinion of qualified dermatologists, many physicians in certain other branches of medicine have not hesitated to express and publish their views that the use of superficial roentgen-ray treatments in "benign" skin conditions is never warranted.

It would seem that any responsible physician or scientific worker should first carefully ascertain whether there is any danger from properly administered superficial roentgen-ray therapy before advocating that innumerable sufferers from skin diseases be deprived of one of the most effective of all therapeutic measures. For example, he should first ascertain whether the sequelae, skin cancers and others, which were reported or observed to have appeared some time after superficial roentgen irradiation, were actually due to that irradiation. (After all, even without any preceding roentgen irradiation, skin cancers are probably the commonest of all cancers.) And if a skin cancer has been shown to be the result of the roentgen irradiation, it must still be ascertained whether the patient was irradiated according to the accepted standards and limits of dermatologic therapy.

Thus, such questions as the following must be answered before the onus for any damage can be placed on irradiation according to the recognized standard dermatologic procedures: Was the patient irradiated by a physician or physicians who did not adhere to the accepted dermatologic standards or who felt justified in administering more than the customary quantities of irradiation? Were technical errors committed when the patient received treatments? Was the patient irradiated by irresponsible "institutes" which are not under the supervision of ethical physicians and which administer roentgen-ray treatments to remove superfluous facial hair? Was the patient one of those unfortunates who deceived successive physicians by not telling them about all the roentgen-ray treatments which had been previously administered by others? Was all the irradiation to the area given only by fully qualified dermatologists?

There are many publications in the world literature describing sequelae produced by superficial and deep roentgen-ray irradiation. However, there are to our knowledge no systematic follow-up studies which would permit conclusions regarding the incidence of roentgen sequelae in statistically adequate samples of patients who have received superficial roentgen irradiation. Most of the reports which have

been published deal with patients who were treated with superficial roentgen rays and who showed sequelae, usually without exact information on the quantity and quality of irradiation the area received, the time period over which this irradiation was administered, and the total number of irradiated patients from which the particular number of patients with sequelae was derived.

Among papers which deal with roentgen sequelae in patients irradiated according to accepted dermatologic techniques are papers by these authors: Miescher and Böhm [1] reexamined 192 patients who had been irradiated for hyperhidrosis of the hands, feet, and axillae. The interval between irradiation and follow-up examination varied from 1 to 22 years. The authors concluded that if the total dose exceeds 1,600 to 1,800 r, late irradiation sequelae may occur. Borak, Eller, and Eller [2] did not find roentgen sequelae in 122 patients who had been irradiated for hyperhidrosis with total doses not exceeding 1,600 r filtered through 2 to 4 mm. Al. The interval that elapsed between treatment and follow-up examinations was not given in the report by Borak and co-workers. Following the work of George C. Andrews, Shafer, Braestrup, and Fisher [3] discussed the importance of the exit dose in the production of roentgen injuries in 52 patients with late irradiation sequelae, 25 of whom had received the customary large doses which are given in the treatment of epithelioma. Pipkin, Lehmann, and Ressmann [4] reexamined 1,000 patients who had been irradiated with 1,000 to 2,720 r in a single dose for plantar warts. The interval between irradiation and follow-up varied from four months to 21 years. No roentgen sequelae had occurred. Among the factors to which these authors attributed the lack of sequelae was the very close shielding of the very small skin field which was treated. The three Montgomerys [5] discussed the occurrence of radiodermatitis in patients irradiated for plantar warts and pointed out that "there is no excuse for use of sequelae-producing dosages of radiation in verruca plantaris."

The existing confusion in this field and the formation of opinions not based on statistically adequate information are exemplified by the statement of Adair [6]:

> Anyone who has ever had even a single dose of low voltage x-ray applied to the skin is a possible candidate for subsequent skin cancer.

Shortly after making this statement, Adair recognized it to be misleading and, therefore, in fair-minded fashion retracted it.[7]

There is, as far as we could find, an absence of adequate statistical data in regard to the eventual fate of skin areas irradiated for various skin diseases by accepted dermatologic techniques.

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1. Miescher, G., and Böhm, C.: Roentgen Therapy of Localized Hyperhidrosis: Follow-Up of 192 Treated Patients, Schweiz. med. Wchnschr. **78**:14, 1948.

2. Borak, J.; Eller, J. J., and Eller, W. D.: Roentgen Therapy for Hyperhidrosis: Observation of 122 Patients, Arch. Dermat. & Syph. **59**:644 (June) 1949.

3. Shafer, J. C.; Braestrup, C. B., and Fisher, J. K.: Relation of Exit Dose and Other Dosage Factors to Roentgen Injuries, Arch. Dermat. & Syph. **59**:472 (April) 1949.

4. Pipkin, L.; Lehmann, C. F., and Ressmann, A.: Treatment of Plantar Warts by Single Dose Method of Roentgen Ray, South. M. J. **42**:193, 1949.

5. Montgomery, A. H.; Montgomery, R. M., and Montgomery, D. C.: Problem of Plantar Radiodermatitis, New York J. Med. **49**:1664, 1949.

6. Adair, F. E.: Prophylaxis of Cancer, Bull. New York Acad. Med. **23**:383, 1947.

7. Adair, F. E.: Prophylaxis of Cancer, Bull. New York Acad. Med. **24**:684, 1948.

The investigations here reported were undertaken in the hope of supplying statistical information on the safety or risks of properly administered dermatologic roentgen therapy through a careful reexamination of the skins of a large group of patients who during the past 5 to 23 years had received superficial roentgen-ray treatments according to the accepted dermatologic dosage schedules.

In particular, we attempted to find the answers to the following questions:

1. When properly administered, do superficial roentgen-ray treatments for benign dermatoses, in the doses and qualities commonly employed by skin specialists in the United States, produce roentgen sequelae?

2. If roentgen sequelae do occur, under what conditions, dosages, etc., are they produced, and what is their incidence and their severity?

3. Do superficial roentgen-ray treatments, as generally given by skin specialists in the United States, predispose to the formation of skin cancers or other malignant changes of the skin?

## METHOD

The Skin and Cancer Unit of New York University Hospital and of the New York University Post-Graduate Medical School (formerly New York Post-Graduate Medical School and Hospital) is probably the biggest part-payment outpatient department for skin diseases in the world, as judged by the number of patients treated, the size of the professional and technical staff, and the number of physicians who are being trained there in the specialty of dermatology and syphilology. For many years the physical therapy section of this unit has treated patients having malignant and benign skin diseases with superficial roentgen rays according to the methods which were introduced by MacKee and developed by him and his co-workers,[8] and which are now almost universally employed by skin specialists in the United States. Moreover, over a period of many years, these treatments have been administered at the Skin and Cancer Unit by many different specialists in dermatology and, under their supervision, by many technical assistants and a large number of graduate physicians in training for specialization in dermatology and syphilology.

The patient material accumulated at the Skin and Cancer Unit thus constitutes an ideal object for the observation of possible roentgen-ray sequelae under conditions in which treatments had been administered according to a prescribed standard method, but by many different physicians and technicians. It seems justifiable to assume that in the large segment of the population treated at this unit careful examination should reveal cases of roentgen sequelae or of skin cancers, if the standard method employed, the technique of administration, and the quantities of irradiation used at the Skin and Cancer Unit tended to produce such sequelae.

The records of 20,230 patients were collected from the record room of the Skin and Cancer Unit. About one-half of these records were from dermatologic patients who 5 to 23 years previously had received superficial roentgen-ray treatments. The other half served as a control group; it consisted of dermatologic patients who 5 to 23 years previously had been under treatment at the unit but who had not received any roentgen-ray treatments. Both the control patients and the irradiated patients were selected without regard to the particular dermatosis for which they had been treated.

Follow-up letters asking them to appear for reexamination were sent to 18,050 of these patients. Up to the time of writing, 2,060 responded to the letters and were reexamined. The letters sent to 8,051 of these patients were returned as not deliverable. It must be assumed that the letters reached the addresses of the remaining 7,939 patients who did not come in for reexamination, although only 357 responded by letter and 405 by telephone. In any event, these 7,939 patients whose letters were presumably delivered were unwilling or unable to return for reexamination.

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8. MacKee, G. M.: Arithmetical Computation of Roentgen Dosage, J. Cutan. Dis. **37**:783, 1919; X-Rays and Radium in the Treatment of Diseases of the Skin, Ed. 2, Philadelphia, Lea & Febiger, 1927.

The reasons given by letter in the case of 357 patients who were unwilling or unable to come for reexamination were as follows:

| | |
|---|---|
| Deceased | 105 |
| Cured | 153 |
| Living out of New York | 50 |
| Under care elsewhere | 23 |
| No specific reasons | 26 |

The reasons given by telephone in the case of 405 patients who were unwilling or unable to come for reexamination were as follows:

| | |
|---|---|
| Deceased | 104 |
| Cured and other reasons | 301 |

It might be argued that some or even many of the 7,177 patients who presumably received letters but did not respond had failed to reply or reappear for examination because of adverse effects of the original roentgen-ray treatments. Therefore, in order to obtain some idea of the reasons the remaining patients had not responded to the letters, 335 visits to the homes of previously irradiated patients and 115 visits to the homes of patients in the nonirradiated group were made by our social workers. The results of these 450 home visits were as follows:

| | X-Ray-Treated Patients | Control Patients |
|---|---|---|
| No. of home visits | 335 | 115 |
| Patients were not found at home and did not respond to a note which was left by the social worker | 164 | 57 |
| Patients had moved away | 81 | 30 |
| Patients stated that they were cured, and thus there was no necessity for their coming for reexamination | 27 | 9 |
| Patients were persuaded to return for reexamination | 51 | 7 |
| Patients stated that they were being treated elsewhere | 6 | 8 |
| Patients did not give specific reasons for not returning | 3 | 2 |
| Patients still had the same condition but found it impossible to return for reexamination | 1 | 2 |
| Deceased | 2 | 0 |

Thus, there was in this sample no evidence that failure to respond to the letters was in any instance due to the previous roentgen treatments. Furthermore, the failures to respond were in essentially the same proportion in the group of nonirradiated patients as in the group of irradiated patients (2,944 of 3,970 failed to reply in the control group, and 2,935 of 3,969 failed to respond in the roentgen-irradiated group). This is, we believe, strong evidence that the lack of response was due to factors not in any way related to the roentgen irradiation.

There were 45 patients who responded to the letter but were excluded from the study and not evaluated because of unreliable information given by the patient, or because the patient had been irradiated in places other than the Skin and Cancer Unit and offices of staff members.

The present report is limited to 2,000 of the reexamined and evaluated group, namely, 1,000 irradiated patients and 1,000 nonirradiated "control" patients.

In order to collect data on this large group of cases, the McBee-Keysort filing system was utilized. The following 143 features of each case were listed on the cards:

Name

Chart Number

Biopsy Number

Photo Number

Age Group, Yr.
- Under 10
- 11-20
- 21-30
- 31-40
- 41-50
- 51-60
- Over 60

Unfiltered X-Rays

No. of Treatments
- 1-5
- 6-10
- Over 10

Total Dosage
- 0-1,000 r
- 1,001-2,000 r
- Over 2,000 r

Period Over Which X-Rays Were Given, Yr.
- 1
- 2
- Over 2

Period Elapsed from Last Irradiation to Present, in Years
- 1-3
- 4-7
- 8-11
- 12-15
- 16-19 and over

Sex
- Female
- Male

Detection of Cancer at First Visit
- Yes
- No

Eye Color
- Hazel
- Blue
- Black
- Brown

Hair Color
- Gray
- Brown
- Black
- Blond
- Red

Skin Color
- Pigmented
- Light pigmented
- Nonpigmented
- Colored

Race
- White
- Black
- Yellow

Continent of Birth
- Europe
- Asia
- Africa
- South America
- North America
- Australia

Roentgen-Irradiated

Not Roentgen-Irradiated

Filtered X-Rays
- Heavy
- Light

Evidence of Roentgen Sequelae
- Atrophy
- Telangiectasia
- Hyperpigmentation
- Depigmentation
- Keratoses
- Ulceration
- Cancer
- Others

Detection of Cancer at Last Visit
- Yes
- No

Side-Effects
- Yes
- No

Exposure to Sun
- Occupational
  - More than normal
  - Normal
  - Less than normal
- Recreational
  - More than normal
  - Normal
  - Less than normal

Occupation
- Housewife
- Clerical
- Farmer
- Miner
- Factory
- Other outdoor work
- Other indoor work

Radiation Used
- X-ray only
- X-ray plus other therapy, e. g., hot quartz lamp, cold quartz lamp, electrodesiccation, electrocoagulation, solid carbon dioxide, etc.

Period Elapsed from First Irradiation to Present, in Years
- 1-3
- 4-7
- 8-11
- 12-15
- 16-19
- Over 19

When Cancer First Detected
- Before 1936
- 1936-1938
- 1939-1941
- 1942-1944
- 1945-1947
- After 1947

Period Elapsed from First Visit to Present, in Years
- 1-3
- 4-7
- 8-11
- 12-15
- 16-19
- Over 19

Every effort was made to exclude mistakes in the calculations of the individual doses and of the total doses of roentgen rays received by each patient. To this end, there were included in the irradiated group only patients who, according to our best information, had received roentgen-ray treatments exclusively in the Skin and Cancer Unit or in both this unit and the private offices of its staff members. Despite this precaution, it is possible that some of these patients may have received roentgen-ray treatments elsewhere as well and have either not remembered or deliberately failed to disclose that such treatments had been received. Any errors of this kind would, of course, make the total dose of roentgen rays as recorded in this report lower than that actually received by the patient. This would obviously make the therapeutic method have an even greater margin of safety than that indicated by the findings here reported.

Without exception, the reexaminations of patients were carried out by qualified specialists in dermatology, who had many years of experience with dermatologic diseases and who were well acquainted with the use of superficial radiation and with the characteristics of cutaneous roentgen-ray sequelae.

## RESULTS

*Results in Irradiated Patients.*—The 1,000 irradiated patients had received superficial roentgen-ray treatments for the following dermatoses: acne, 197; "eczema," 139; psoriasis, 36; skin cancer, 101; "neurodermatitis," 80; miscellaneous dermatoses, 447.

The doses of irradiation which had been given at the individual sittings varied from 37.5 r in benign dermatoses to 1,800 r in skin cancers.

The number of treatments administered per site varied from 1 to 20.

The number of sites irradiated in the individual patient ranged from 1 to 25, with an average of 2.1 sites per patient.

There were 763 patients in whom no individual dose exceeded 85 r, and there were 237 to whom some individual doses of more than 85 r had been administered.

Seven hundred twenty-four patients received a total of between 150 and 1,000 r; 201, a total of between 1,000 and 2,000 r, and 75, a total of over 2,000 r. Four

hundred fifty-eight patients had received their treatments 5 to 7 years previously; 296 patients, 8 to 11 years previously; 220 patients, 12 to 15 years previously; 21 patients, 16 to 19 years previously; and 5 patients more than 20 years previously.

Eight patients were under 10 years of age at the time of reexamination; 26 patients were 11 to 20 years old; 164 were 21 to 30 years old; 225 were 31 to 40 years old; 214 were 41 to 50 years old; 193 were 51 to 60 years old, and 170 were over 60 years of age.

*Roentgen Sequelae.*—Roentgen sequelae were found in 28 patients. In 10 of these roentgen irradiation only had been employed; and in the remaining 18 other methods of physical and surgical treatment had been used in addition.

A. Roentgen-Ray Sequelae in Patients Irradiated with Individual Doses of More Than 85 r (Such as Are Used in Malignant Skin Conditions and Certain Other Tumors and Cutaneous Lesions): Of the 28 patients in whom roentgen sequelae were observed, 26 had been irradiated with these larger doses. The sequelae observed in these patients were as follows:

| No. of Patients Irradiated | Yr. Since Roentgen Therapy |
|---|---|
| Skin Cancer (0 cases) | .. |
| Ulceration (0 cases) | .. |
| Atrophy, Telangiectasia, Depigmentation, Hyperpigmentation, Keratoses (4 cases) | |
| 1 | 14 |
| 1 | 9 |
| 1 | 8 |
| 1 | 7 |
| Atrophy, Telangiectasia, Depigmentation, Hyperpigmentation (5 cases) | |
| 1 | 16 |
| 1 | 14 |
| 1 | 12 |
| 1 | 6 |
| 1 | 5 |
| Atrophy, Telangiectasia, Depigmentation (12 cases) | |
| 1 | 12 |
| 1 | 10 |
| 3 | 9 |
| 5 | 8 |
| 1 | 7 |
| 1 | 5 |
| Atrophy, Hyperpigmentation, Depigmentation (1 case) | |
| 1 | 10 |
| Atrophy, Telangiectasia (4 cases) | |
| 1 | 8 |
| 2 | 7 |
| 1 | 6 |

The quantities of roentgen-rays received by the 26 patients in whom the usual limiting dose for benign inflammatory diseases had been deliberately exceeded were as follows:

| No. | Dose | No. of Patients and Yr. Since Roentgen Therapy: Patients | Years |
|---|---|---|---|
| I. Patients Treated for Skin Cancer | | | |
| 1 | 5,000 r (10 × 500 r filtered) | .. | 12 |
| 2 | 4,800 r (8 × 600 r unfiltered) | 1 | 8 |
| | | 1 | 6 |
| 1 | 4,500 r (1,800, 1,500, and 1,200 r unfiltered) | .. | 8 |
| 1 | 3,900 r (900 r and 5 × 600 r unfiltered) | .. | 8 |
| 4 | 3,600 r (12 × 300 r unfiltered) | 2 | 5 |
| | | 2 | 7 |
| 1 | 3,600 r (3 × 1,200 r unfiltered) | .. | 9 |
| 3 | 3,000 r (10 × 300 r unfiltered) | 2 | 8 |
| | | 1 | 10 |
| 1 | 2,850 r (1,350 r and 1,500 r unfiltered) | .. | 14 |
| 1 | 2,700 r (3 × 900 r unfiltered) | .. | 10 |
| 1 | 2,700 r (900 r and 3 × 600 r unfiltered) | .. | 8 |
| 1 | 2,550 r (1,650 r and 900 r unfiltered) | .. | 14 |
| 1 | 2,400 r (2 × 900 r and 600 r unfiltered) | .. | 7 |
| 3 | 1,800 r (1,800 r unfiltered) | 1 | 7 |
| | | 1 | 8 |
| | | 1 | 9 |
| 1 | 1,800 r (2 × 900 r unfiltered) | .. | 6 |
| 3 | 1,500 r (1,500 r unfiltered) | 2 | 9 |
| | | 1 | 12 |
| II. Patient Treated for Keloids | | | |
| 1 | 4,543 r (11 × 413 r filtered) | .. | 16 |

In contrast to the above 26, there were 211 other patients who displayed no roentgen sequelae whatsoever (despite the fact that they also had received single or multiple doses each of more than 85 r for malignant growth of the skin or for certain other dermatoses in which larger individual doses are deliberately employed, e. g., keloids, verrucae vulgares, and furuncles). Of these patients without sequelae: 5 had verrucae vulgares, and furuncles). Of these patients without sequelae: 5 had received a total of more than 4,000 r; 21, a total of 3,000 to 4,000 r; 8, a total of 2,000 to 3,000 r; 42, a total of 1,000 to 2,000 r, and 135, a total of less than 1,000 r.

B. Roentgen Sequelae in Patients Irradiated for Benign Skin Conditions with Individual Doses of 85 r or Less: It is, we believe, particularly noteworthy that only 2 of the 28 patients in whom roentgen sequelae were observed had been irradiated for benign dermatoses, and that in these the sequelae were slight. The types of sequelae observed, the dosage, and the time intervals in these two patients were as follows:

PATIENT 1.—A woman, aged 28 years, with acne vulgaris had received 1,200 r (16 × 75 r unfiltered) 13 years ago and showed slight atrophy, telangiectasia, and depigmentation. This patient was blond and blue-eyed, has had more than average exposure to sunlight, and had received additional treatments with cold quartz irradiation and solid carbon dioxide.

PATIENT 2.—A man, aged 59, with chronic "eczema" on the dorsa of the hands had received 1,087.5 r (5 × 37.5 r and 12 × 75 r unfiltered) 10 years ago and showed atrophy, hyperpigmentation, and a few scattered superficial keratoses. This patient, brown-haired and brown-eyed, was an unemployed actor who had more than average sun exposure. He spent most of his time for more than 20 years fishing and gardening.

In contrast to these two patients with mild sequelae, there were 761 other patients who also had received fractional doses of roentgen irradiation for benign skin conditions but who showed no roentgen sequelae whatsoever. Of these patients without sequelae, 12 had received a total of 37.5 to 150 r; 618, a total of 150 to 1,000 r; 130, a total of 1,000 to 2,000 r, and 1, a total of more than 2,000 r.

Cancer Formation in Irradiated Patients: All patients were carefully examined for the presence of skin cancers both in previously irradiated and in nonirradiated skin areas. These examinations revealed one epithelioma in each of six patients. Five of these epitheliomas were located in skin areas which had never been irradiated! The remaining epithelioma was located in a previously irradiated area on the left breast of a 56-year-old salesman, but the skin of this region showed no changes characteristic of roentgen sequelae, and only one treatment of 150 r unfiltered had been administered to this area. For these reasons, and taking into consideration the high incidence of "spontaneous" cancers of the skin, the possibility that this epithelioma was due to the roentgen rays appears to us most unlikely as compared with the possibility that it appeared "spontaneously" and by chance in an area which had been irradiated.

*Results in Nonirradiated Patients.*—The 1,000 control patients, i. e., the group of nonirradiated patients, had been treated by other than roentgenologic measures for the following dermatoses: acne vulgaris, 90; "eczema," 117; psoriasis, 75; skin cancer, 140; "neurodermatitis," 38; miscellaneous dermatoses, 540.

Cancer Formation in Nonirradiated Patients: All the patients who had not received any roentgen irradiation were also carefully examined for the presence of

skin cancers. These examinations revealed one epithelioma in each of nine patients. (As compared with one epithelioma in each of only six patients of the irradiated group!)

COMMENT

The results of the studies thus far completed indicate that 28 of 1,000 irradiated patients showed roentgen sequelae. Twenty-five of these patients had received the roentgen treatments for skin cancers, in which, in order to achieve a cure, one may deliberately administer doses that are expected to produce some degree of roentgen sequelae in a certain percentage of cases. Another of these patients presented a keloid for which 4,543 r had been administered and in which roentgen sequelae also were to be expected when the treatments were given. However, from the cosmetic and functional viewpoint, the roentgen sequelae produced were more acceptable than the keloid for which the irradiation was given. (It must be said that the standard doses of roentgen rays used nowadays in cases of keloid are considerably smaller than the dose of 4,543 r [filtered] which had been given to this patient 16 years ago.)

In addition to the 26 patients with roentgen sequelae who had received roentgen rays in the treatment of their skin cancers or keloid, there were 211 patients who also had received individual doses of irradiation each of more than 85 r, but in whom sequelae had not developed. These figures show that about 1 of every 9 of the 237 patients who received individual single doses of irradiation larger than 85 r exhibited some sort of roentgen sequelae. Taking only the 76 patients in this group who received single doses of more than 85 r and total doses exceeding 1,000 r, the calculation shows that 1 of every 4 had some sort of sequelae.

It must be stressed, however, that even in this group of 26 patients with sequelae, all the changes were, without exception, relatively mild and of purely cosmetic significance; there was no instance of ulceration or cancer formation. The lowest total amount of irradiation in these 26 patients with sequelae was 1,500 r unfiltered, given in a single session.

In addition to the patients who had received individual doses of more than 85 r, there were two patients with benign dermatoses who had received small fractional doses, i. e., individual doses of 85 r or less and who, nevertheless, showed some signs of roentgen sequelae.

One of these was a patient treated for acne vulgaris, who 13 years ago had been given 16 treatments, 75 r each unfiltered, making a total of 1,200 r.[9] In 12 of these treatments both sides of the face had been irradiated, and in 4 treatments the exposure had been "full face," i. e., one exposure over the midportion of the face.

The other patient had "eczema" and, 10 years previously, had received 17 treatments, namely, 5 treatments of 37.5 r unfiltered and 12 treatments of 75 r unfiltered to the dorsa of the hands, making a total of 1,087.5 r. This patient, at the same time, received treatments to the palms of $3 \times 37.5$ r each unfiltered, making a total of 112.5 r.

In contrast to the two patients in this series in whom some roentgen sequelae had developed after treatment for benign dermatoses, there were 761 patients who

9. Before 1939 the value of the roentgen unit was such that 300 r was the skin-erythema dose with the factors generally employed at our Unit and ¼ erythema dose was considered to be 75 r unfiltered; since then the value of the roentgen unit has been officially lowered, so that ¼ erythema dose comprises 85 r at present (i. e., skin-erythema dose equals 340 r).

also had received irradiation in fractional individual doses of 85 r or less for benign dermatoses but who did not exhibit roentgen sequelae. From this, one might infer that 1 of every 380 patients irradiated for benign dermatoses with small fractional doses of roentgen rays may show some slight sequelae. However, this figure needs further correction; for more minute analysis of the data shows that not a single one of the 618 patients who had received doses of roentgen irradiation totaling between 150 and 1,000 r displayed sequelae, whereas 2 of the 131 patients who had received more than 1,000 r had some sequelae. Thus, no patient who had received a total of 1,000 r or less in small fractional doses of 75 to 85 r or less had sequelae, whereas about 1 in every 65 patients who had received a total of more than 1,000 r in fractional doses for benign dermatoses displayed roentgen sequelae. However, it may be open to question whether the roentgen rays did more than contribute a share of the damage even in the two patients with benign dermatoses who had received a total of more than 1,000 r. It should be pointed out here that both the patients who exhibited roentgen sequelae after receiving the small fractional doses also had more than average exposure to sunlight over a period of many years. It is also noteworthy that in neither of these patients was there the development of any serious sequelae such as radiation ulcer or epithelioma. In view of the fact that no patients were included whose roentgen treatments had been concluded less than 5 years ago, and that many were examined as late as 8 to 20 years after conclusion of treatment, it may be assumed that most of the sequelae which were going to develop in this series were discovered. Since careful dermatologic examination after five years or more failed to reveal even suspicious mild or prodromal changes (dryness, scaling, pigment changes, etc.), it appears to us unlikely that any significant number of our patients will still show even mild sequelae and highly improbable that severe sequelae will still appear.

In our opinion, the figures presented permit the inference that, in the large sample of the population here investigated, superficial roentgen-ray treatments as generally given by dermatologists in the United States did not predispose the irradiated areas and persons to the formation of skin cancers, for among the 1,000 irradiated patients epitheliomas were found in only 6 (and in only 1 of these in an irradiated area), while among the 1,000 nonirradiated control patients epitheliomas were found in 9.

At the present stage of this study, the three previously listed major questions with which this investigation is concerned can be tentatively answered as follows:

Question 1: When properly administered, do superficial roentgen-ray treatments for benign dermatoses, in the doses and qualities commonly employed by skin specialists in the United States, produce roentgen sequelae?

Answer: In the large sample of the population here investigated superficial roentgen-ray treatments in fractional doses of 85 r given up to a total of 1,000 r did not produce roentgen sequelae. Among patients who receive superficial roentgen-ray treatments in fractional doses totaling more than 1,000 r units, but not beyond the total in general dermatologic use today, some manifestations of sequelae may be expected in about 1 of 65 patients. These exceptional patients are likely to be those who, in addition to the roentgen irradiation, have had years of repeated, excessive, or unusually prolonged exposures to sunlight.

Question 2: If roentgen sequelae do occur, what is the severity of the changes observed?

Answer: The sequelae produced in the two patients who had received single exposures in doses of no more than 85 r each but to a total of more than 1,000 r, as well as in the 26 patients who had received larger individual doses, were purely cosmetic in import and were not those of the most serious type, i. e., they did not include cancers or radiation ulcers.

Question 3: Do superficial roentgen-ray treatments, as generally given by skin specialists in the United States, predispose to the formation of skin cancers or to other malignant conditions of the skin?

Answer: In the sample of the population here investigated there is no evidence that such treatments predispose the irradiated skin areas or persons to the formation of epitheliomas or other malignant alterations.

## INFERENCES

Based upon the large sample of the population here investigated and upon the findings on reexamination of 1,000 irradiated patients and 1,000 nonirradiated control patients, we infer as follows:

1. Superficial roentgen-ray treatments as given by dermatologists in the United States, in the doses necessary for the cure of cancers and other malignant growths of the skin, produce mild roentgen sequelae in about 25% of cases.

2. There is no evidence that any sequelae are produced by totals of 1,000 r or less of superficial roentgen-ray treatments in the fractional doses and in the qualities generally employed by dermatologists in the United States for the treatment of benign dermatoses (such as acne vulgaris, "eczema," "neurodermatitis," and psoriasis). When total doses of more than 1,000 r (in our series the range was between 1,000 and 2,630 r) are given, it may be expected that about 1.5% of patients will exhibit roentgen sequelae which are relatively mild and of only cosmetic importance.

3. There is no evidence that cancers, roentgen ulcers, or any other dangerous sequelae are produced, even with the very largest doses which most dermatologists today consider permissible for benign dermatoses (total, 1,400 r).

## ABSTRACT OF DISCUSSION

Dr. G. Marshall Crawford, Brookline, Mass.: I have had the privilege of going through this material, and I assure you that Dr. Sulzberger was unable to present more than a fraction of what he has. The work reported on here represents a far greater amount of effort than might be apparent to the casual listener, as many of you know. To start with 20,000 cases and net 2,000 actually usable observations is no mean accomplishment. It surely would not have been possible without a generous grant and thereby paid personnel. Three of us at the Massachusetts General Hospital, Boston, have tried to do a similar study, limited to patients with acne, and it has been a tedious process. The results presented today are exactly those that would be expected by a dermatologist experienced in roentgen therapy. One might even say that the data have been too conservatively presented. That would be my only real criticism.

About 10% of the 1,000 patients in the roentgen-treated group had cancer. These 101 instances could properly be the subject of a separate consideration, and a study of the remainder would more clearly answer the queries postulated as initiating motives in the study. The separation of cancer patients from this large sample of dermatologic patients receiving roentgen therapy would deemphasize such a statement as, "Taking only the 76 patients in this group who received single doses of more than 85 r and total doses exceeding 1,000 r, the calculation shows that 1 of every 4 had some sort of sequelae." Those figures are correct but could easily be misinterpreted and unduly emphasized.

It was subsequently pointed out that the doses necessary for the cure of malignant growths of the skin produced mild roentgen sequelae in about 25% of the patients. With consideration of this fact strictly in the light of cancer therapy, it is surprising how little postirradiation change was evident. Seven patients received between 1,500 and 1,800 r; the other 18 were given totals of 2,400 to 5,000 r, in divided doses. My cancer therapy routine calls for totals of 2,000 to 36,000 r, in one to six divided daily doses, as required by various factors. I expect irradiation sequelae and rarely fail to find them within a few months. It seems entirely reasonable to separate this cancer group from any survey of a group with roentgen-treated benign dermatoses.

A survey of roentgen therapy of cancer of the skin at the Massachusetts General Hospital a few years ago indicated that the highest percentage of success was obtained when a single dose of low-voltage therapy of 2,500 to 2,800 r was administered. When divided doses were used, 4,500 r in one week was the suggested dose.

The 900 patients with benign dermatoses in Dr. Sulzberger's series were treated with fractional doses of 85 r or less. Only 2 of the 28 patients who exhibited irradiation sequelae had received this fractional treatment. Thus, it could be said that 1 in 450 patients treated for nonmalignant cutaneous disease by properly administered roentgen therapy could be expected to show any sequelae. It was properly emphasized, however, that these two patients received a total of more than 1,000 r, and this bears out the wisdom of sensible limitation of total dosage, even with fractional therapy. Excessive sun exposure had occurred in both of these cases, and this tends further to exonerate the x-ray treatment.

The value of a control group is beautifully illustrated by the finding of nine carcinomas of the skin among the 1,000 nonirradiated patients as against six in the roentgen-therapy group. Actually, only one of the six patients had received irradiation on the area where the epithelioma was found, but the amount of that treatment had been only a single half-erythema dose.

Nothing in the control data refers to changes in the skins of nonirradiated patients which might approximate roentgen sequelae. Ages were not listed for this control group, but, if it was comparable with the x-ray group, more than half of the patients were past 40 years of age. Among 500 such subjects some must have had a bit of atrophy, telangiectasia, pigmentary alterations, or a few keratoses.

One factor to be borne in mind is that this group of 2,000 observations was made on patients living in the New York area. If a similar study were possible in the Southwest, more cutaneous changes classifiable as radiation sequelae would inescapably be found in both the treated and the untreated groups. Nevertheless, it could be predicted that the relative percentages of irradiation sequelae and carcinomas would be similar.

Our follow-up survey at the Massachusetts General Hospital was confined to acne patients who were irradiated 5 to 20 years earlier. We could prevail upon so few to return that use of office patients was required to enlarge the group to about 60 patients. The dosage levels were between 600 and 1,450 r per exposed area. The only change possibly related to irradiation sequelae was telangiectasia and probably this was explainable by other causes. Certainly, it seemed insufficient to incriminate roentgen therapy. Details of these observations will appear elsewhere. Our data obviously confirm those given here today.

The series of questions which were posed at the initiation of the study appear to be well answered, and the statistics given are good documentation of the relative innocence of properly administered roentgen treatment. The inferences offered by the authors seem fully warranted.

Dr. Paul E. Bechet, Elizabeth, N. J.: Dr. Sulzberger's statistics are of great practical and forensic interest. I was very active at the old Skin and Cancer Hospital from 1909 to 1942 and chief of the clinic from 1928 to 1932; I am glad to hear that roentgen sequelae were so little noted in my regimen. The dosage at that time consisted of 75 r to either side of the face, without filtration, at 60 to 80 kv., not exceeding 12 treatments.

My purpose in entering into the discussion on Dr. Sulzberger's paper is to record a clinical observation of much forensic interest, which, as far as I know, has not been previously mentioned, that is, the appearance of atrophic lines and superficial linear scars, symmetrically distributed on the cheeks and angles of the mouth, strongly suggestive of roentgen sequelae. They were apparently due to small, healed, indurated acne lesions in linear formation on these locations in patients who had never received roentgen therapy.

DR. J. HERBERT MITCHELL, Chicago: I wish to express my great appreciation of this paper because after a great many years of practice I was involved in an amusing kind of legal case. In 1932 I treated a boy 9 years old with two small doses of the roentgen rays on the chest. Over the years periodically some lawyer would call me up and say that the mother of the boy was bringing suit. Thanks to Dr. F. E. Senear, the case was promptly thrown out of court. The suit had been outlawed as regards the mother, but for the boy, since he was a minor at the time of treatment, there was no statute of limitation. When he was 25, the case came to trial. The fact was that at puberty a hairy pigmented nevus had developed over the sternum, with a most beautiful growth of hair.

One interesting case, a slide from which was shown at a meeting of the American Academy of Dermatology and Syphilology, was that of a boy who had been given 1,250 r, according to the written statement of a small hospital radiologist. There was total alopecia at the time I first saw the patient. I was much concerned about the regrowth of hair, but he now has a good growth, and the prognosis seems to be very good. I should like to ask Dr. Sulzberger about a paper which appeared in *Science* some time ago and which has caused a great deal of concern on the part of my patients. They have read that in two or three generations after x-ray therapy the patient's descendants will be having monsters; I should like to know how many monsters Dr. Sulzberger has turned up in this survey.

DR. A. C. CIPOLLARO, New York: Dr. Sulzberger and his associates have presented a great deal of detailed information. Reviewing those thousands of cases must have been a tremendous job. This study probably was undertaken because of a statement that a single small superficial dose of x-rays is capable of producing cancer, which appeared in the *Bulletin of the New York Academy of Medicine* in an article written by a leading cancer expert. That statement raised the ire of the members of the Section of Dermatology and Syphilis of the New York Academy of Medicine, and a committee met with the cancer expert. In a later issue of the *Bulletin,* the statement was retracted. The members of the committee, besides Dr. Sulzberger and myself, were Dr. Lewis, Dr. Sharlit, and Dr. Costello.

This report is particularly gratifying to me because the material reviewed by Dr. Sulzberger and his associates were patients who were treated during a period that I was in charge of the department. All this work was done by me or by my associates under my supervision. The authors compiled the statistics, and they show that a remarkably small number of patients received irradiation injuries. However, we must bear in mind that every time we give a dose of x-rays we either inhibit or destroy cells; therefore, we must adhere to the modern trend of using less and less x-rays for the treatment of inflammatory and nonmalignant dermatoses. When we treat malignant growths of the skin with x-rays or with radium we must adhere to the principle that enough irradiation be used to destroy neoplastic cells. That amount of irradiation will lead to irradiation sequelae. Therefore, all successfully treated cancer patients should show some degree of radiodermatitis of the treated area. The statistics presented here reveal that only one-fourth of the group of patients with cancer so treated showed irradiation changes. Perhaps a review of these patients will disclose a higher percentage of irradiation damage. The incidence of radiodermatitis in the patients treated for nonmalignant dermatoses appears to be too high. Perhaps I did not understand the essayist correctly.

A comparison is made in the incidence of cancer in an irradiated and a nonirradiated group. I don't think this means anything, because one can make the statistics come out anyway one pleases. The fact that the nonirradiated group showed a much higher percentage of cancer than the irradiated group indicates nothing in my opinion. I think that the most important point of this paper is that, when x-rays are administered properly with proper spacing and by well-trained dermatologists, they are safe and do not increase the incidence of cancer. There is no excuse for the person who turns the x-ray machine on the face of a girl with acne and then proceeds to write a letter, answer the telephone, or direct his attention away from the patient without turning off the apparatus. The administration of a dose of x-rays requires the full attention of the person giving the treatment.

DR. GEORGE C. ANDREWS, New York: I am familiar with this material, having heard it before at some of the New York society meetings, and I have had time to reflect upon it. It is a splendid piece of work; its results seem almost too good to be true. I still do not understand just how many patients with acne were treated. I do not think there is any question about cancer arising from x-rays on other parts of the body. The treatment of acne with x-rays is the

main factor to be considered. In that connection the dose of x-rays and the omission of the midface exposure are important. There is no doubt that in the older techniques there was an overirradiation of the midportion of the face.

I am glad that Dr. Sulzberger mentioned the work of Dr. Shafer, who was with me at the time that she reviewed the cases of radiodermatitis during the past 20 years at the Presbyterian Hospital, New York. There we had 160 cases of radiodermatitis. About half of these were produced by the treatment of cancer, diseases of the thyroid, and other serious ailments, but not dermatoses. The other half (85) were the result of treatment for benign dermatoses. These were reviewed with reference to the exit dose as a factor in the production of chronic roentgen injuries. Fifty-six patients were treated by irradiation, usually over prolonged periods, for conditions in which superficial therapy to opposing surfaces is still frequently used. Radiodermatitis was present frequently in this group on the middle part of the face and the extremities, where the exit dose is high, and it may have been an additional factor in the production of irradiation damage to the skin.

Over half of these patients presumably were treated, as far as we could determine from the records, by radiologists, general practitioners, or others in the treatment of dermatologic conditions. In other words, less than 40 cases during the past 25 years could possibly be attributed to dermatologists. Considering the frequency with which x-rays are used, it is evidence that very few cases of chronic radiodermatitis are attributable to dermatologists who use modern techniques, and I am sure that Diplomates of the American Board of Dermatology and Syphilology will not cause any harmful effects with their use of x-rays.

In connection with acne and the frequency of cancer on the face, I think that it is of interest that carcinogenic substances have been found in smears of horses' smegma, and it is possible that in the human sebaceous glands as persons grow older some of the steroids may become carcinogenic through the action of sunlight or ultraviolet light in connection with the changes of age. There is no doubt that acne patients, as a rule, get more sunlight and ultraviolet light than the average patient does, and sunlight is perhaps a more important factor in causation of cancer of the face than x-rays are.

DR. C. GUY LANE, Boston: For many years we have needed evidence that would help establish the total amount of x-rays which can be given safely in fractional doses. For many years I have used the factor of 1,200 r as an upper limit of such irradiation, but it would seem from Dr. Sulzberger's figures that we could perhaps use 1,400 r with safety. At the same time, we should exercise great care in the selection of patients to whom this amount is given. I say this in view of the fact that in one instance I have seen telangiectasia develop in a blond boy to whom I had given just over 600 r in fractional dosage some time before. He was 16 years of age and had a moderate acne. I saw him some years later but have not seen him since, so that I do not know what has happened in the meantime. However, I am a firm believer in the inevitability of later changes once the process has started; thus, if one sees telangiectasia which can be ascribed to irradiation, then I feel sure that at a later age the sequence of changes which Dr. Sulzberger has outlined will be very apt to occur. It is my belief, therefore, that for blond persons especially the choice of a lower dosage of x-rays is extremely important.

I further believe in the individuality of dosage for each patient and that numerous cases of acne or other nonmalignant conditions will often respond to less than the maximum dosage of irradiation. Just as there are factors in the machine which gives the dosage, so there are factors in the individual person, such as site, sex, type of disease, and depth, which should aid in determining the dosage (*New England J. Med.* **221**:769-773, 1939). While the dosage for the disease needs to be considered, the dosage for the individual patient also needs consideration.

The matter of contraindications is also an extremely important item in determining the dosage (ARCH. DERMAT. & SYPH. **61**:426-432 [March] 1950).

It seems to me that the 1.5% irradiation changes appearing in the group given fractional treatment of nonmalignant skin disease is too high. If that is a true figure, it would be an argument against the use of irradiation generally for nonmalignant cutaneous disease. However, if figures for the skin cancer group are included in these statistics, then there would, of course, be irradiation changes as an end-result. I was rather surprised that Dr. Sulzberger included patients with skin cancer in this study, because we expect to find irradiation changes, i. e., atrophy, scarring, and telangiectasia, in practically all such patients whether treated intensively or by fractional dosage.

DR. EVERETT C. FOX, Dallas, Texas: The object of this study was to determine whether low-voltage superficial roentgen rays as employed by dermatologists may produce undesirable results or predispose the skin to cancer formation. Careful review of 1,000 patients who had received superficial x-ray therapy did not reveal evidence of an increased tendency to cancer formation. In recent years the statement has been made that a single exposure to x-rays may predispose to cancer development. While this statement was retracted at a meeting of the New York Academy of Medicine, it has not been retracted generally. Many of us in the practice of dermatology have had the opportunity of seeing patients who received x-ray therapy many years previously, and we observed that sequelae were extremely infrequent in patients treated by dermatologists. Although these observations have been made by many of us, this paper provides a careful investigation of a large number of patients subjected to statistical analysis and will be valuable to us.

Pigmentation and telangiectasia may develop in persons exposed to sun and wind, particularly farmers, seafarers, and proponents of sunbathing. These cutaneous changes resulting from sun are frequently seen in the Southwest, and the pigmentation and keratoses may closely resemble changes produced by x-irradiation. Dr. Sulzberger and his associates have given us factual information on a large number of patients treated and observed many years after roentgen therapy, and they have found that there is no increase in the development of cancer.

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: Nine years ago a housewife, then 30 years of age, came to me with lichen planus. There were several hypertrophic lesions, located particularly on the anterior aspects of the knees. I gave her x-ray therapy totaling 675 r. The doses were either 100 or 125 r at 90 kvp. with inherent filtration only. I may believe her statement that she received no treatment from anyone else. A year ago she came to me with notable telangiectasis and atrophy of the treated areas. During the preceding six months a wart-like lesion had developed on the left knee. This had grown at the time I saw her to a verrucoid tumor 12 mm. across. I excised it. It was a squamous-cell carcinoma.

One year ago a 7-year-old boy was brought to me with tinea capitis. For two years local applications had been used, but no other therapy. My cultures yielded Microsporum audouini. X-ray epilation was performed, using the five-point technique with 375 r and no added filter. The results were satisfactory. This child was brought to me three weeks ago with a 10-mm., firm, smooth, bald, elastic, nonpigmented hemispheric nodule located on the occipital scalp, on which hair had long since regrown normally. I excised this tumor, finding it histologically to be a fibrosarcoma.

I have given x-ray therapy to perhaps 10,000 persons, among whom these two *"post hoc"* instances only will have to be taken for what they are worth. No medical agent can be given a patient without hazard. One cannot prescribe an aspirin without the possibility of ill-effect. I would rather receive 1,000 r from a competent dermatologist for what he believed to be a good reason than an injection of penicillin, with respect to the dangers involved.

DR. MAURICE J. COSTELLO, New York: Dr. Sulzberger's paper is a tribute to the dermatologists who treated these patients during the past 20 years at the Skin and Cancer Hospital. There is one fact to be explained in his paper: To me it seems unlikely that 1,000 patients could receive roentgen rays over a long period without having received further roentgen irradiation at some other time for a recurrence of the condition. New York is a large city with many dermatologists. Patients go from one physician to another, and frequently roentgen rays are administered a second and even a third time. I think, too, that it is important for this group to go on record to determine, so to speak, whether a patient should receive roentgen rays for acne or not, what the optimal weekly and total dose is, and so forth. Such studies should be made for other dermatoses as well. I, for one, believe that roentgen irradiation properly administered when indicated is still the most effective single method of treatment for severe long-standing acne vulgaris.

As Dr. Cipollaro pointed out, there are certain statements made that patients with acne should never receive roentgen irradiation. Dr. Sulzberger mentioned that 1,400 r can be administered with no risk at all, as attested to by his facts and figures.

I believe that epitheliomas of the face occur as a result of excessive ill-advised irradiation for dermatologic conditions. These epitheliomas appear in the middle vertical third of the face almost directly in the midline on the bulbous portion of the nose, the lips, and the skin. I have

treated a number of epitheliomas in these locations, and Dr. Andrews has given the explanation for them. They are caused by incorrect technique in centering the beam over the zygomatic arch when the tip of the nose is on the same plane, thus permitting a greater exit dose through those parts, causing radiodermatitis with subsequent epitheliomas.

DR. C. FERD LEHMANN, San Antonio, Texas: I should like to emphasize that the effects of x-ray are dependent not only upon the physical factors used, such as anode-skin distance, voltage, or quality of the rays, but upon the method in which the total dosage is given, such as its duration, its fractionation, and the size of the portal through which it enters the skin. Therefore, the novice must not construe the statements in the paper as endorsing the application of 1,000 r in any other technique than that which is stated by the essayists.

The paper analyzes the sequelae up to 23 years after use of a certain technique in which all the factors of dosage have been fairly constant. It is gratifying to see a report showing that the effective dosage of x-rays for an inflammatory condition can be safely administered. All conservative therapists desire to use the minimal effective doses, and it is hoped that this study will lead to others like it.

We should all study our late results and aim toward prevention of any unsatisfactory residual atrophies when treating any benign or inflammatory skin conditions. I have in mind the doses of irradiation to hemangiomas in babies. This is a condition in which a study of the late effects from various techniques of irradiation is sorely needed. I feel that doses to angiomas should be well below those mentioned in some of the articles in present-day literature.

I should like to ask Dr. Sulzberger if he has seen any late ill-effects in his series from epilating doses applied to ringworm of the scalp.

DR. M. B. SULZBERGER, New York: I should like to express my particular gratitude to Dr. Crawford for a most thoughtful and eminently constructive discussion. We tried to be as conservative as we possibly could, and I accept his criticism that we may have been too conservative in including our patients with skin cancers receiving x-ray treatments. However, for the reasons which Dr. Lehmann has just outlined so well, I thought that in this situation we were a little like Caesar's wife and that it behooved us to be scrupulous in evaluating the harmful effects which might appear from this type of treatment.

Our decision to include cancers was based principally on two considerations. The first was that we wanted to find out what sequelae occur when the skin receives doses of superficial roentgen rays exceeding those which are generally given in treating benign dermatoses; the second was that, as has been pointed out, this study required a good deal of financial support and the Atomic Energy Commission naturally was interested in finding out the upper, limiting, or damaging dose of superficial roentgen rays. For these reasons we included figures on results of this type of soft irradiation in the higher dosages, such as dermatologists generally use only in treating skin cancers.

Dr. Lane, I am sorry that I did not make myself sufficiently clear. The incidence of 1.5% sequelae referred only to those patients who had received more than 1,000 r, in other words, to those patients who had received roentgen-ray doses in the range from 1,000 to 2,630 r. As a matter of fact, with ordinary methods of treatment as given for benign dermatoses and excluding the patients treated for preexisting malignant growths of the skin, there were only 2 instances of even mild sequelae in the whole group of 1,000 patients.

Dr. Everett Fox has rightly called attention to the fact that repeated exposures to sunlight produce changes which are in the same direction as, and may be mistaken for, the changes produced by roentgen rays. This must, of course, always be borne in mind when one is examining skins for evidence of possible damage due to roentgen rays.

Concerning Dr. Bechet's statement I want to thank him publicly for assisting in making this study possible, just as I wish to thank Dr. Charles M. Williams, Dr. Eugene Traub, and all the others who worked at the old Skin and Cancer Unit. In addition and in particular, I want to express gratitude to Dr. George M. MacKee and to Dr. Cipollaro, who was formerly in charge of our Section on Radiation Therapy. Not only is Dr. Cipollaro to be congratulated on the record of this Section, but he is also right in his statement that we should not use this method of treatment when it is not needed. And Dr. Richard Sutton is, of course, equally correct in emphasizing this once again. However, I cannot agree with those who state that the nonirradiated control group adds nothing to this study. I think the control group is really

the heart of the study, because it shows what happens to the skin of an equivalent sample of the same population throughout the years without x-rays. It presents evidence that cancer formation was, to say the least, just as common and rapid in the skins of this control nonirradiated group as it was in the group in which irradiation was given.

Dr. Costello mentioned the possibility of our patients receiving additional irradiations elsewhere. We carefully excluded all patients that had been irradiated anywhere except in the Skin and Cancer Unit and/or in the offices of the staff members when we could get the office records. All others were excluded, and that was one of the factors which reduced the yield of cases we considered statistically valid. Of course, despite our care, errors may have been made. Some patients may not have told us about irradiation received elsewhere either through forgetfulness or because they deliberately withheld the information. But any and all such errors have made our conservatism in evaluating the safety of x-rays even greater, because they made the dosage actually received greater than that which our records showed. Thus, the direction of any possible error would make treatment with x-rays even safer than it appears to be in our results.

Exactly as Dr. Lehmann said, in relation to benign dermatoses, we set out to study just the one standard type of fractional dosage treatment that had been outlined by MacKee, namely, ¼ skin-erythema dose or less given once weekly. I do not remember offhand the number of patients with acne that we had in our series, but it was probably a very high percentage of all cases, because acne was the commonest disease treated by x-rays during these years.

Sunlight indubitably produces the same kind of changes as x-rays, but whether there is a summation or a potentiation of the damage by sunlight and the damage by x-rays is, as far as I know, not yet proved. However, such summation is highly probable, and for the present at least, one must assume that one cannot safely give as much irradiation to sandy-haired, blue-eyed persons exposed to sunlight as one can to dark-haired, dark-eyed persons who live indoors. I am sure that in Texas and perhaps in California and Florida the effect of sunlight must be taken into consideration in determining the limiting dose of x-rays. But it would be an error to think that persons in New York live like moles and abide entirely in cellars and subways. The pictures which I now show you are of the Coney Island beach and will give you an idea of the incidence of exposure to sunlight as well as the extent of the skin areas exposed to sunlight by many of the population from which our Skin and Cancer Unit patients are drawn. In that population, 1,000 r of unfiltered roentgen rays given in fractional doses of no more than 85 r weekly has apparently failed to produce even the mildest sequelae.

# TREATMENT OF PYODERMAS WITH PENICILLIN 92

## Comparison with Neomycin and Bacitracin

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SOME TIME ago the director of the Hektoen Institute, which is the division of research of the Cook County Hospital in Chicago, enlisted our cooperation for a study of several new antibiotic agents. The Institute was interested particularly in a new type of penicillin, *l*-ephenamine penicillin G (penicillin 92).[1] It has an antibacterial spectrum which in vitro parallels that of penicillin G, but which differs from it in one important respect. *l*-Ephenamine penicillin G is thought to have hypoallergenic properties similar to those attributed to penicillin O.[2]

Although there are many excellent agents available for the topical treatment of pyogenic infections of the skin, each of them has certain limitations. The better ones are the broad-spectrum antibiotics, but even among these there is none that has proved to be effective in all cases. All the antibacterial drugs on occasion may produce allergic reactions, while some actually may irritate the skin. The older antibacterial products, such as ammoniated mercury, usually achieve results much too slowly, and others, such as methylrosaniline chloride (gentian violet), although they effect a cure, have cosmetic shortcomings. Consequently, we readily agreed to undertake the clinical investigation with *l*-ephenamine penicillin G, particularly since there were available also for a comparative study limited supplies of other relatively new antibiotic agents—neomycin, bacitracin, and fradicin, the last being an antifungal agent.

*l*-Ephenamine penicillin G has the formula 1,2-diphenyl-2-methylaminoethanol penicillin.[3] It is a large-molecule-type salt resembling penicillin procaine in unit dosage, absorption, and excretion.

Bacitracin [4] is produced by a particular strain of Bacillus subtilis, and, while it has a qualitative antibacterial spectrum approximating that of penicillin G against

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From the Hektoen Institute, Cook County Hospital, and the Department of Dermatology, Northwestern University Medical School.

Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

1. Kadison, E. R.; Ishihara, S. J., and Walters, T.: A New Form of Penicillin with Anti-Allergic Properties, Am. Pract. & Digest Treat. **2**:411 (May) 1951.

2. Volini, I. F.; Shlaes, W. H., and Felsenfeld, O.: Use of Penicillin O in Patients Hypersensitive to Penicillin G, J. A. M. A. **143**:794 (July 1) 1950.

3. The *l*-ephenamine penicillin G ("compenamine") used in this study was supplied by Commercial Solvents Corporation, New York 17.

4. Johnson, B. A.; Anker, H., and Meleney, F. L.: Bacitracin: A New Antibiotic Produced by a Member of the B. Subtilis Group, Science **102**:376 (Oct. 12) 1945.

Gram-positive organisms, it is effective occasionally against organisms that are resistant to the latter. It is particularly suitable for topical application because of its relatively low index of sensitizing properties and the fact that it is used for systemic administration only infrequently.

Neomycin [5] is derived from Streptomyces fradiae, and it, too, has a broad antibacterial spectrum. It is especially active against Gram-negative strains of organisms. Toxic reactions (particularly eighth-nerve damage) have been reported [6] from its parenteral administration, but no toxic manifestations have been recorded to date from its topical application.

Fradicin [7] also is obtained from S. fradiae as a fraction of its antibiotic complex. It is an antifungal agent which is reported to be active in vitro against various saprophytic and pathogenic fungi.

## METHOD AND MATERIAL

Our plan was to apply the aforementioned drugs to a variety of pyodermas in order to determine both the therapeutic effectiveness and the potential sensitizing properties of each. At the same time the predominant organisms from each case, as identified by culture studies, were subjected to sensitivity tests against the various antibiotics. This was done not so much to indicate the choice of a drug—for treatment usually had to be instituted before results of the sensitivity tests were ascertained—but to furnish an explanation for any therapeutic failures that might occur. Finally, ointments containing various combinations of the antibiotics were used in order to see whether the therapeutic effectiveness would be enhanced by broadening the antimicrobial spectrum.

Laboratory experiments and preliminary clinical trials showed that the optimum doses of each of these drugs for application in ointments are as follows:

| Drug | Dose |
|---|---|
| *l*-Ephenamine penicillin G | 10,000 units/gm. |
| Neomycin | 10,000 units/gm. |
| Bacitracin | 1,000 units/gm. |
| Fradicin | 50 γ/gm. |

When the antibiotics were combined in an ointment, the doses were as follows:

| Drug | Dose |
|---|---|
| *l*-Ephenamine penicillin G | 10,000 units/gm. |
| Bacitracin | 500 units/gm. |
| Neomycin | 5,000 units/gm. |
| Bacitracin | 1,000 units/gm. |
| Fradicin | 50 γ/gm. |

Petrolatum was used as the vehicle because it produced an ointment that remained stable at room temperature.

One hundred patients, 10 of whom were hospitalized and 90 of whom were ambulatory, were treated with one or another of these preparations. At the first examination cultures for pyogenic organisms were made, and the patient was furnished with a tube of ointment to be applied four times daily for initial treatment. The cultures were made by applying a sterile swab to the most active part of a lesion and then storing the swab in a tube containing brain-heart infusion broth or isotonic sodium chloride solution. After the clinic period—usually within two hours—the material was delivered to the laboratory, where additional tubes of

5. Waksman, S. A., and Lechevalier, H. A.: Neomycin, A New Antibiotic Active Against Streptomycin-Resistant Bacteria, Including Tuberculosis Organisms, Science **109**:305 (March 25) 1949.

6. Waisbren, B. A., and Spink, W. W.: A Clinical Appraisal of Neomycin, Ann. Int. Med. **33**:1099 (Nov.) 1950.

7. Swart, E. A.; Romano, A. H., and Waksman, S. A.: Fradicin, An Antifungal Agent Produced by Streptomyces Fradiae, Proc. Soc. Exper. Biol. & Med. **73**:376 (March) 1950.

semiliquid brain-heart infusion broth and blood agar plates were inoculated from it. After routine isolation of pure cultures, these were subjected to sensitivity tests to different antibiotics by the serial tube-dilution method.[8]

## CULTURES AND SENSITIVITY TESTS

Successful cultures were obtained from 91% of the 100 patients.[9] Since they were obtained primarily for the performance of sensitivity tests, classification of the cultures was limited to bacterial groupings, and they were subclassified only into hemolytic and nonhemolytic strains. In these 91 cultures there were 83 strains of organisms identified, including 23 strains of beta hemolytic streptococci, 51 strains of hemolytic staphylococci, and 9 strains of nonhemolytic staphylococci. The group of nonhemolytic staphylococci generally are considered to be nonpathogenic. Yet the results from treatment of the patients from whom these organisms were recovered, and particularly from treatment of patients with primary infections of the skin, were so uniformly excellent that further investigations are now under way

TABLE 1.—*Results of Sensitivity Tests*

| Organism Cultured | Antibiotic Inhibition, Units/Cc.* | Number of Strains | | |
|---|---|---|---|---|
| | | *l*-Ephenamine Penicillin G | Bacitracin | Neomycin |
| Beta-hemolytic streptococci (23 strains) | 1 | 20 | 16 | 9 |
| | 1-25 | 1 | 5 | 13 |
| | 50+ | 2 | 2 | 1 |
| Hemolytic staphylococci (51 strains) | 1 | 32 | 12 | 26 |
| | 1-25 | 5 | 34 | 11 |
| | 50+ | 14 | 5 | 12 |
| Nonhemolytic staphylococci (9 strains) | 1 | 5 | 2 | 2 |
| | 1-25 | 1 | 6 | 1 |
| | 50+ | 3 | 1 | 6 |

* Key to symbols: 1, highly sensitive; 1-25, moderately sensitive; 50, not sensitive.

to determine the role of nonhemolytic staphylococci in the development of pyodermas.

The results, as recorded in Table 1, showed that of the organisms subjected to sensitivity tests to the various antibiotic agents 57 strains were highly sensitive to *l*-ephenamine penicillin G, as compared with 37 strains highly sensitive to neomycin and 30 strains highly sensitive to bacitracin.

## RESULTS OF TREATMENT

Of the 100 patients studied, 70 had primary infections (62 pyogenic, 8 fungal) and 30 had secondarily infected dermatoses.

At first, the medicaments employed were selected alternately. It was soon noted that results from treatment with *l*-ephenamine penicillin G were so uniformly excellent that it was used thereafter for all the patients, the other drugs being reserved for any patients who might not respond to *l*-ephenamine penicillin G. Of the 100 patients, 50 were treated with *l*-ephenamine penicillin G alone, 20 with neomycin,

8. Ishihara, S. J.: Microbial Sensitivity Determinations in Small Laboratories, Laborat. Digest **14**:8 (March) 1951.

9. Tests were performed by S. J. Ishihara, B. S.

5 with bacitracin, and 25 with various mixtures of the drugs. In the last group, 11 of the patients were treated with a mixture which contained *l*-ephenamine penicillin G.

Of the 70 patients with primary infection, none failed to respond favorably to treatment, regardless of which antibiotic or combination of antibiotics was used.

TABLE 2.—*Treatment of Primary Infectious Dermatoses**

| Diagnosis | *l*-Ephenamine Penicillin G, 10,000 Units/Gm. | | | | Neomycin, 10,000 Units/Gm. | | | | Bacitracin, 1,000 Units/Gm. | | | | *l*-Ephenamine Penicillin G, 10,000 Units/Gm.; Bacitracin, 500 Units/Gm. | | | | Neomycin, 5,000 Units/Gm.; Bacitracin, 1,000 Units/Gm.; Fradicin, 50 γ/Gm. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI |
| Impetigo | 18 | 18 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ecthyma | 6 | 6 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 2 | 0 | 1 | 0 | 1 | 0 |
| Pustular folliculitis | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Coccogenous sycosis | 2 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mixed infections (pyodermas) | 12 | 11 | 1 | 0 | 5 | 4 | 1 | 0 | 2 | 1 | 1 | 0 | 3 | 2 | 1 | 0 | 2 | 1 | 1 | 0 |
| Dermatitis streptogenes | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Otitis externa | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 43 | 40 | 3 | 0 | 11 | 7 | 4 | 0 | 5 | 4 | 1 | 0 | 8 | 5 | 3 | 0 | 3 | 1 | 2 | 0 |

* Key to symbols: No., number treated; C, cured; I, improved; NI, not improved.

TABLE 3.—*Treatment of Secondary Infected Dermatoses*

| Diagnosis | *l*-Ephenamine Penicillin G, 10,000 Units/Gm. | | | | Neomycin, 10,000 Units/Gm. | | | | Bacitracin, 1,000 Units/Gm. | | | | *l*-Ephenamine Penicillin G, 10,000 Units/Gm.; Bacitracin, 500 Units/Gm. | | | | Neomycin, 5,000 Units/Gm.; Bacitracin, 1,000 Units/Gm.; Fradicin, 50 γ/Gm. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI | No. | C | I | NI |
| Infectious eczematoid dermatitis (nummular dermatitis) | 3 | 0 | 2 | 1 | 5 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 |
| Atopic dermatitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 3 | 1 | 2 | 0 |
| Neurodermatitis (localized) | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Seborrheic dermatitis | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dermatitis venenata | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stasis dermatitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Stasis ulcers | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | 0 | 3 | 0 |
| Perlèche | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pemphigus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Dermatophytosis pedis | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Paronychia | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Verruca vulgaris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 7 | 1 | 5 | 1 | 9 | 1 | 8 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 2 | 0 | 11 | 1 | 10 | 0 |

Fifty-seven patients were cured completely, and 13 showed a considerable amount of improvement (70 to 90%), usually within three days. Of all the preparations, *l*-ephenamine penicillin G effected the highest percentage of cures.

Of the 30 patients with secondarily infected dermatoses, 29 had distinct benefit from treatment with the antibiotics under study. Not only was the infectious element in each of these cases eliminated, but also the underlying diseases were improved considerably. The results confirmed the observation of Leifer and Steiner

in their study with diiodohydroxyquinoline that the "control of the infectious element has often ameliorated the basic, noninfectious component of [an] eruption."[10]

The 10 hospitalized patients were studied by the "paired comparison"[11] method. Triantibiotic ointment (neomycin, bacitracin, and fradicin) was applied to one limb, and another agent, such as sulfonamide or ammoniated mercury, to the other limb. The results from use of triantibiotic ointment were far superior to those obtained with the other preparations. There were no failures from treatment, and the period of hospitalization was shortened considerably. In one case of pemphigus vulgaris the application of the antibiotic mixture (neomycin, bacitracin, fradicin) produced results that were especially gratifying, for the usual foul odor was eliminated, and the patient was made much more comfortable.

In contrast to the results observed in primary infections, in the group of secondary infections *l*-ephenamine penicillin G showed no particular superiority over the other antibiotics.

In six patients the sensitivity tests demonstrated their practical value. All six had failed to respond to initial treatment satisfactorily, and when treatment was changed to use of another of the antibiotics (as indicated by the results of sensitivity tests) there was complete cure. This group included two patients with impetigo of the face and two with pustular folliculitis of the scalp and forearms who failed to respond to initial treatment with neomycin and then were cured by *l*-ephenamine penicillin G. In one case each of sycosis of the skin and pyoderma of the hand the results were reversed. Neomycin was more effective than *l*-ephenamine penicillin G. In the one case of infectious eczematoid dermatitis of the hand which failed to improve, sensitivity tests showed the organisms to be resistant to all the antibiotics under investigation.

Fradicin, 50 γ per gram, was used in only eight cases of fungal infections. It failed to effect any improvement in them despite trials that were more than adequate. Five of the cases were of tinia capitis due to Microsporum audouini, one was of tinea corporis, and two were of dermatophytosis pedis due to Trichophyton mentagrophytes (gypseum).

## REACTIONS

An allergic-contact-type eczematous reaction was observed in only one case; it resulted from neomycin. *l*-Ephenamine penicillin G did not produce a single instance of irritation or cutaneous sensitization among the 61 patients on whom it was used.

## SUMMARY AND CONCLUSIONS

*l*-Ephenamine penicillin G (penicillin 92), a new antibiotic agent thought to have hypoallergenic properties, was used by itself with striking success for the topical treatment of 61 patients with pyogenic infections of the skin. Neomycin, bacitracin, and various combinations of the two with *l*-ephenamine penicillin G were used for 39 patients. The number of patients studied was too small to permit sweeping con-

10. Leifer, W., and Steiner, K.: Diiodohydroxyquinoline in Dermatologic Therapy, Arch. Dermat. & Syph. **62**:46 (July) 1950.

11. Sulzberger, M. B.; Baer, R. L.; Kanof, A., and Lowenberg, C.: Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin, J. Invest. Dermat. **7**:227 (Oct.) 1946.

clusions, but in this small series all the antibiotics proved to be almost equally effective and well tolerated even by infected eczematous skins, for only one case of sensitization occurred, and that, from neomycin. Of the three antibiotics, *l*-ephenamine penicillin G was definitely the most effective for primary infections but was slightly less effective for secondary infections than bacitracin and neomycin in combination. The antibiotics usually produced improvement rapidly (within three days), and in six cases, when considerable improvement did not occur quickly, sensitivity tests usually suggested a change to another antibiotic agent which proved more effective. The sensitivity tests supported the clinical impression that *l*-ephenamine penicillin G was the most effective antibiotic under study, because, of the 83 organisms tested, 57 strains were highly sensitive to this drug, in comparison with 37 strains markedly sensitive to neomycin and 30 to bacitracin.

Theoretically one might expect a combination of *l*-ephenamine penicillin G, with its wide antibacterial spectrum against Gram-positive bacteria, and neomycin, with its wide antibacterial spectrum against Gram-negative organisms, to have a broader or additive antimicrobiotic effect upon pyodermas and to produce superior results. Yet the results from use of various combinations of the three antibiotics in 25 cases were not particularly superior to those from use of the agents singly.

Fradicin, although it was used in only eight cases of fungal infections, failed to effect any improvement in them.

104 S. Michigan Ave.

## ABSTRACT OF DISCUSSION

DR. W. W. DUEMLING, San Diego, Calif.: The study on this new drug was conducted with a threefold purpose: first, the determination of the effectiveness and sensitizing properties of *l*-ephenamine penicillin G as compared with bacitracin and neomycin; second the determination of sensitivity of the organisms cultured from the patients under observation to the various antibiotics, and third, the possibility of enhancing the therapeutic effectiveness of antibiotics by combination of one with another.

From the data presented, it is evident that *l*-ephenamine penicillin G is superior to the other antibiotics in the treatment of primary infections and does not produce cutaneous sensitization. However, in the group of secondary infections it showed no particular superiority. A possible explanation for this might be that neomycin and bacitracin in combination act against both Gram-positive and Gram-negative organisms, exerting a destructive as well as inhibitive effect against sensitive organisms. *l*-Ephenamine penicillin G, on the other hand, kills only those organisms which are in the process of active multiplication.

The sensitivity tests supported the clinical impression that *l*-ephenamine penicillin G was the most effective antibiotic under study. Not infrequently, however, differences have been noted between in vitro and in vivo antibacterial studies, because the former measure bacteriostatic rather than bactericidal activity, and cultures under the two conditions are not exactly the same.

The possibility of enhancing the therapeutic effectiveness of antibiotics by using them in combination has recently aroused interest among a number of investigators. In Dr. Rattner's experiments the combination of *l*-ephenamine penicillin G and bacitracin failed to show any additive or synergistic effect. It is possible, as shown by recent experiments (Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin, *Arch. Int. Med.* **87**:349 [March] 1951), that some of the newer antibiotics antagonize the bactericidal action of penicillin. The suggestion has been offered (Hunter, T. H.: Speculation on the Mechanism of Cure of Bacterial Endocarditis, *J. A. M. A.* **144**:524 [Oct. 14] 1950) that since penicillin kills only those organisms which are in the process of active multiplication the presence of another agent—such as aureomycin or chloramphenicol (chloromycetin®)—renders

them static (inhibits but fails to kill); then organisms are no longer killed by penicillin. The use of various combinations of antibiotics needs to be explored further before any definite statements can be made concerning the most effective combinations.

Up to the present no antibiotic has been found to have fungicidal properties, and, in the few cases in which it was tested, fradicin is apparently no exception.

Dr. J. Lowry Miller, New York: Since my colleagues and I have had experience with different antibiotics, one after another, we have come to the conclusion that for the usual pyogenic skin infections they are almost equally effective. The advantages of each are dependent upon other factors about which more is being learned each year.

The development of resistance to different antibiotics by the organisms is of great importance. Our group feels that testing of susceptibility of the organisms present in each case to the various antibiotics yields valuable information.

At the coming meeting of the American Medical Association, we have an exhibit demonstrating a relatively simple method for determining the causal organisms and, at the same time, their susceptibility to the various antibiotics. This method is suitable for routine office use.

I was particularly interested to note that Dr. Rattner did not find superior results from the combination of antibiotics, as might be anticipated on theoretical grounds. Many of these combinations are being introduced at this time. More work must be done to prove or disprove superiority in results from use of combinations of antibiotics.

Dr. James R. Webster, Chicago: My associates and I are able to confirm part of Dr. Rattner's findings on the basis of work done at Children's Memorial Hospital, Chicago. After the report by veterinarians on the effectiveness of fradicin against certain fungi in animals, we used this agent in five cases of tinea capitis due to Microsporum audouini and in three cases due to Microsporum lanosum. After three months of continual treatment, we observed virtually no improvement in any of the cases.

# MILKERS' NODULES

## Report of Ten Cases

RUBEN NOMLAND, M.D.
AND
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MILKERS' nodules in man is a virus disease of the skin acquired, in most instances, from milking cows who are infected with natural (not vaccinia or genuine) cowpox. Natural cowpox is a virus disease of the teats and the udders of milch cows and is common among dairy cows in Iowa and probably throughout the United States. Becker [1] was the first to report milkers' nodules in this country; he described four cases in residents of northern Minnesota and Wisconsin. After hearing Becker's presentation, Beck [2] reported three cases from Delaware, and a few years later Green [3] reported one case from Louisiana. Green stated that he had seen many cases of the disease and had recognized it as an occupational disease of milkers. Hester and associates [4] studied an epidemic in a dairy herd in Illinois; they saw one case of milkers' nodules and heard of several others.

We have had the opportunity to observe 10 cases of milkers' nodules and have performed biopsies in 3 and virus studies in 2 cases, but the results of the virus studies proved to be of a negative character.

The term cowpox as used in both medical and veterinary literature is confusing because it seems that at least two distinct viruses cause cowpox in cows. Hagan [5] mentions this fact, but his distinction of the two viruses is unclear. Udall [6] differentiates them much better, referring to "natural" cowpox and to "genuine" or vaccinia cowpox. Natural cowpox produces milkers' nodules in man, but this virus has not yet been isolated and studied in the laboratory. The virus of vaccinia cowpox, one

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Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

From the Department of Dermatology and Syphilology and the Department of Bacteriology, State University of Iowa.

1. Becker, F. T.: Milkers' Nodules: Report of 4 Cases, J. A. M. A. **115**:2140 (Dec. 21) 1940.

2. Beck, J. R.: Milkers' Nodules: A Clinical Note, Delaware M. J. **12**:180 (Aug.) 1940.

3. Green, M. T.: Milkers' Nodule, New Orleans M. & S. J. **97**:13 (July) 1944.

4. Hester, H. R.; Boley, L. E., and Graham, R.: Studies on Cowpox: I. An Outbreak of Natural Cowpox and Its Relation to Vaccinia, Cornell Vet. **31**:360 (Oct.) 1941.

5. Hagan, W. A.: The Infectious Diseases of Domestic Animals, with Special Reference to Etiology, Diagnosis, and Biologic Therapy, Ithaca, N. Y., Comstock Publishing Company, Inc., 1943, pp. 526-529.

6. Udall, D. H.: The Practice of Veterinary Medicine, Ed. 4 (revised), Ithaca, N. Y., Author, 1943, pp. 519-523.

of the best-studied viruses in the laboratory, rarely causes cowpox in cows except when explosive epidemics occur in herds which have been infected by recently vaccinated persons.

The clinical course and epidemiology of natural cowpox in cows are inadequately described in the texts on veterinary medicine available, but personal communications from two local veterinarians, correspondence with two teachers of veterinary medicine,[7] and the information received from the patients seen with milkers' nodules are sufficient to give a composite picture of the disease in cows. The disease is endemic and common in the milking herds in Iowa and probably throughout the United States. The two local veterinarians consulted each stated that he knew of 10 to 20 infected farm herds a year in his practice. They did not offer an opinion on the way in which the disease was spread from farm to farm but felt that it was spread through the herd by the milker, as epidemics are unknown in beef cattle.

The earliest lesion in cows is a papule about 5 mm. across, located on the teats and surrounded by a red areola 20 mm. in diameter. The papule rapidly becomes pustular, or a pinhead- to pea-sized (1- to 6-mm.) whitish area develops on the surface. The center may be umbilicated or not, but soon the lesion develops a crust which is usually wet, thick, and up to 15 mm. across. If the crust falls off, or more commonly comes off when the cow is milked, there is left a granulating ulcer 6 to 15 mm. across which heals slowly, producing a slight scar, so that the complete evolution of a single lesion takes at least two weeks. The lesions are not numerous, ranging from two to as many as a dozen, occasionally more, and they may be in several stages of evolution. The lesions are located on the teats or on the udder at the base of the teats. The disease in the average case lasts six weeks to 3 or more months in the individual cow; the epidemic in a herd may last up to 18 months, spreading slowly from cow to cow, but, as a rule, most of the cows in a milking herd eventually become infected. The symptoms and complications of the disease are minimal; farmers seldom seek veterinary care in uncomplicated cases and usually treat the disease with antiseptic ointments. Both veterinarians consulted felt that reinfection of the same cow occurred occasionally but that relapses after apparent cure were more frequent. Neither knew of a human case of milkers' nodules, although four of our patients were from the immediate vicinity. The small number of human cases of milkers' nodules compared with the great number of cows having natural cowpox indicates that the disease is not highly contagious to man. Each veterinarian had seen one epidemic of vaccinia or genuine cowpox in cows, but they were not able to give any information except that they thought the lesions on the cows' teats and udders were about the same as those in natural cowpox.

There are several reports in the literature showing that recently vaccinated human beings can infect cows with vaccinia and cause epidemics of vaccinia cowpox in the cows; the infected cows then infect, usually on the hands, unvaccinated human beings who handle them. The best example of these localized epidemics comes from Uruguay, where there has been an intensive campaign to vaccinate a previously

7. Irwin, J. G., and Howe, E. C.; Merchant, I. A. (Professor and Head of the Department of Veterinary Hygiene, Iowa State College, Ames, Iowa), and Hagan, W. A. (Dean, New York State Veterinary College, Ithaca, N. Y.): Personal communications to the authors.

unvaccinated population. Abente Haedo [8] reported one such epidemic in detail and knew personally of eight other similar ones. Briefly, a recently vaccinated dairy worker infected one or a few of the cows, but another unvaccinated worker, who subsequently came down with cowpox, transmitted the infection to almost 100% of the cows. These cows then infected all five of the unvaccinated workers who handled the cows, but not the two workers who had been vaccinated previously. The lesions on the cows were pock-like and consisted of herpes-zoster-like vesiculopustules with a red halo, which became crusted and healed. He did not state the number of lesions present in the cows, but in the case pictured by Boerner [9] in an epidemic in the United States there were 20 crusted lesions on two teats. The cows were ill, their milk production fell off, but they recovered in a few weeks. The lesions in the men numbered 5 to 20, were located chiefly on the hands, and consisted of pock-like lesions which dried to form crusted lesions. There were constitutional symptoms, headache, malaise, and fever, which lasted some time. Gray [10] reported a similar epidemic in England. The disease caused by each of the viruses of cowpox is distinctive, but in cows both diseases are commonly called cowpox; occasionally writers in the medical literature refer to milkers' nodules as cowpox, as did McCloy.[11]

## REPORT OF CASES

CASE 1.—A 41-year-old man stated that a bluish lesion about the size of a matchhead (2 mm.) developed on a finger two weeks prior to his examination, and that it had grown to 12 mm. in diameter in that time. The lesion was not painful except when he struck it. He was unsuccessfully vaccinated at the age of 18, but revaccination two years later was successful. He thought that he had had cowpox at 15 years of age, but he did not remember the details. Six weeks previously one of his cows had had lesions on her teats, which he described as four flat, scabbed-over, slightly thickened places about the size of a fingernail.

The patient's lesion, located just distal to the proximal interphalangeal joint of the third finger on the left hand, was 12 mm. in diameter (Fig. 1*A*) and was elevated about 3 mm. It was a firm bluish-red nodule with a slight crust in the center. It was not painful to ordinary handling, in spite of the fact that there were several red lymphangitic streaks on the flexor aspect of his forearm. The epitrochlear node was slightly enlarged and slightly tender, but the axillary nodes were not. A good-sized piece was removed for biopsy and virus studies. He was given aureomycin for a week with no apparent healing, and because the aureomycin treatment did not improve the lymphangitis he was given two injections of depot penicillin, which controlled the cellulitis in four days but did not influence the nodule. No further treatment was given; by the end of the second week the lesion was one-half healed, and by the fourth week it was practically well except for slight redness and pigmentation.

CASE 2.—A 28-year-old man, who had never been vaccinated, had dermatitis herpetiformis and arsenical pigmentation and keratoses. He had been milking cows who had pustules and wart-like lesions on the teats, and he acquired the present lesion two weeks before he was seen. It started as a small boil, then slowly enlarged and lost its pustular and inflammatory aspect. The lesion was located on the dorsal aspect of his right wrist, just over the head of the radius.

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8. Abente Haedo, F.: Epizootía de cowpox en un ganado lechero, producido por la inoculación accidental de un hombre, recientemente sometido a la vacunación antivariólica: Contaminación consecutiva de todo el personal del establecimiento que no había sido vacunado: Tratamiento por la fiebre artificial, Arch. urug. med. **34**:252 (March) 1949.

9. Boerner, F.: An Outbreak of Cow-Pox, Introduced by Vaccination, Involving a Herd of Cattle and a Family, J. Am. Vet. M. A. **64**:93 (Oct.) 1923.

10. Gray, J. S. M.: Note on an Outbreak of Cowpox Affecting Animals and Milkers at Dairy Farms, M. Officer **70**:61 (Aug. 21) 1943.

11. McCloy, A.: A Case of Cow-Pox, Brit. M. J. **1**:362 (March 8) 1941.

It was a nontender, firm, not very inflamed, slightly crusted lesion, 10 mm. in diameter, and was surrounded by a large area of redness. A specimen was removed for biopsy and virus studies, and the lesion healed in 17 days. Several weeks after the nodule was healed, the patient was successfully vaccinated.

Case 3.—A 16-year-old boy, not previously vaccinated, milked cows who had wart-like lesions on their teats and udders. His lesions had begun about three weeks before he came in for examination. At that time he had two firm, purplish-red, elevated nodules, each several millimeters in diameter, covered by a moist crust and located on the base of the right thumb (Fig. 1*B*) and on the right index finger. A biopsy was done; he was vaccinated with smallpox vaccine, and a week later he had a good "take" in the vaccination. When he was last seen,

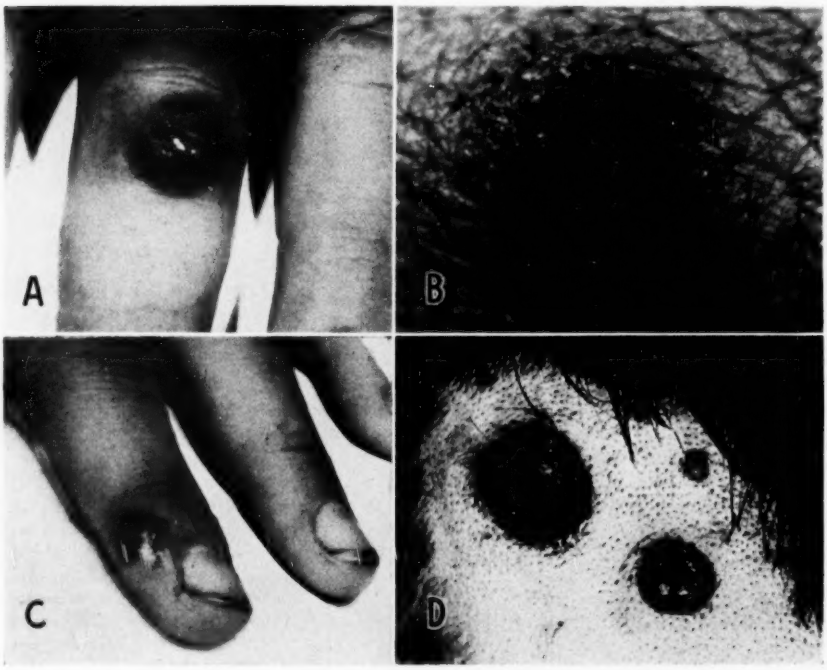


Fig. 1.—Clinical variations in milkers' nodules: *A*, the nodule in Case 1 is dark red and firm, with serum oozing from the center. *B*, the lesion in Case 3, enlarged somewhat, is the commonest type and has a medium-red base with a verrucoid scaly crust in the center. *C*, the lesion in Case 6 is a somewhat smooth elevated one which probably has fluid beneath the tense epidermis. *D*, the lesions in Case 7 closely simulate a granuloma pyogenicum.

four weeks after the first visit, the nodules were completely healed except for a small fibrous thickening.

Case 4.—A woman in her fifties had milked cows who had "warts" on their udders at that time and intermittently for several years previously. Her lesion had begun on the chin two weeks before she consulted us, and it had grown slowly up to the time of examination but was asymptomatic. She had an elevated firm lesion on the chin, 9 mm. in diameter and elevated 3 mm. It was somewhat verrucous in the center and was purple-red and firm, but there were several small pustules at the edge. It healed without scar in about five weeks. She had been vaccinated in childhood, and she believed a boy who helped with the milking had lesions on his hands, but she was not aware of their type or duration.

CASE 5.—A boy, aged 10 years, had milked cows who were known to have cowpox, consisting of small vesicular, pustular, or crusted lesions 2 to 9 mm. in diameter on the teats and udders. The cows had been infected for two months, and the herd had had previous epidemics of cowpox, but no human cases had appeared previously. Four weeks before he was seen here the lesion had started as a pimple on the right ala nasi, and in two weeks it developed to a smooth swelling with a crust and later became wart-like. The lesion was 12 by 9 mm., elevated 6 mm., and located on the right ala of the nose. It was very much like an ordinary wart, except that the base was purple-red. The lesion healed in one month and left a scar. He had been vaccinated at the age of 6 years, and a recent revaccination was unsuccessful.

CASE 6.—A boy, aged 14 years, milked for six weeks a cow who had four to seven lesions on each of her teats. They were described as being the same color as the teat, elevated about 3 to 6 mm., and somewhat rough on the surface. Eighteen days before his first visit to the hospital, the patient noted a small lesion on the left middle finger which looked like a "blood" blister. This had increased in size up to the time he was examined. The lesion was located on the side of the finger just distal to the terminal interphalangeal joint, was 10 mm. in diameter (Fig. 1*C*), and was elevated somewhat. The border of the lesion was reddish-purple, and the center was yellowish, not definitely pustular, but there was probably fluid beneath the epidermis. The lesion was healed when he was seen three weeks later, and only slight redness remained. There is no information on whether he had been vaccinated against smallpox.

CASE 7.—A man in his sixties stated that he did not have anything to do with cows in the course of his farming activities, and that his cows had no known disease. Four weeks before his first visit, a reddish lesion developed on the back of his neck; shortly after the first one a second appeared, and 18 days later the third one came. He had three lesions within the hair-line on the back of his neck (Fig. 1*D*). The largest was 16 mm. in diameter and elevated about 3 mm.; the smallest was 5 mm. in diameter and proportionately elevated. The largest lesion was purple-red and quite firm; the smallest was medium red and less hard. The smallest lesion was not crusted; the largest had a bloody crust, and the middle-sized one was partly crusted. The appearance was not unlike that of a granuloma pyogenicum. The lesions healed in about four weeks without noticeable scar. He had been vaccinated in childhood.

CASE 8.—A 19-year-old woman had milked a cow who had had large warts on her teats for some months. About 18 days before the patient's first visit she had noted a red papule on the dorsum of the left third finger over the terminal interphalangeal joint. This enlarged slowly and was not painful, so that on the first examination she presented a firm, apparently fluid-filled lesion, 8 mm. across and with the appearance of a synovial lesion. After a few days it became definitely inflammatory and larger, and the roof was removed to reveal a granulating base which healed in a short time. Biopsy of the material removed showed simple inflammation. She had been successfully vaccinated a few months previously.

CASE 9.—There are very few data on this farmer, a man past 60 years of age, who was seen once only. On the cutaneous aspect of the upper and lower lip on the right he had two lesions which had started as blisters one month previously. They were now two firm reddish-purple lesions 12 mm. in diameter and elevated about 3 mm., somewhat suggestive of a granuloma pyogenicum.

CASE 10.—This man was also a farmer past middle age who was seen only on one occasion. Three weeks prior to his visit his lesions had started as smooth pimples which had enlarged to the present size. The two lesions were firm red inflammatory nodules 13 mm. in diameter, with a crust in the center, located on the knuckle of the third finger and the web of the right thumb.

## ANALYSIS OF DATA

In seven of the eight cases in which the fact was recorded, the cows had lesions on teats or udders, but the descriptions given by the patients were not at all uniform. Most of them referred to the cows' lesions as warts, but two had noted vesicles or pustules on the cows. In all instances, when noted, only one or a few of the cows of a herd had lesions. The vaccination status was recorded in seven patients, and five had been successfully vaccinated as children or young adults; in

two of these the vaccination was done as recently as a few months and four years before the milkers' nodules appeared. Of the two patients not vaccinated, one having active infection with milkers' nodules was successfully vaccinated while he still had an active nodule, and the second was vaccinated after the nodule was healed. These facts indicate that vaccination against smallpox does not prevent acquisition of milkers' nodules and that persons with active milkers' nodules can be successfully inoculated with vaccinia.

Fig. 2 (Case 2).—Medium-high-power view showing parakeratotic crust over a dried-up vesicle in epidermis. Characteristic long thin rete pegs are well shown, extending into confluent infiltrate around numerous newly formed capillaries.

As one would expect, the nodules were located on the areas directly exposed to infection or on the neck or face. In five patients the lesions were located on the fingers and in one each on the wrist, chin, cutaneous part of the lips, ala nasi, and nape of the neck. The mean duration of the disease before the first visit was three weeks, and the lesion was healed in most cases three weeks later. The shortest complete duration of the lesion was five weeks, the longest, eight weeks, and the mean duration, six weeks. The number of nodules varied from one to three, with six patients having single lesions, three having two lesions, and one having three nodules.

While there was some variation in the histories, most of the lesions started as a small, inflamed area that the patient thought was a simple infection, a beginning

furuncle, or some similar benign lesion. The lesions, instead of healing as minor infections do, enlarged and became definitely nodular and in two weeks were elevated, firm, and usually not very tender nodules with a mean diameter of 12 mm. Four patients presented elevated reddish-purple nodules with a moderate amount of crust in the center; one nodule was almost like a verruca; one was verrucous in the center; two had the appearance of a granuloma pyogenicum; one probably had fluid beneath the epidermis, and one was a thick-walled fluid-containing lesion with the appearance of a synovial lesion. There was no instance of widespread eruption of any sort, several cases of which were reported in the early literature.

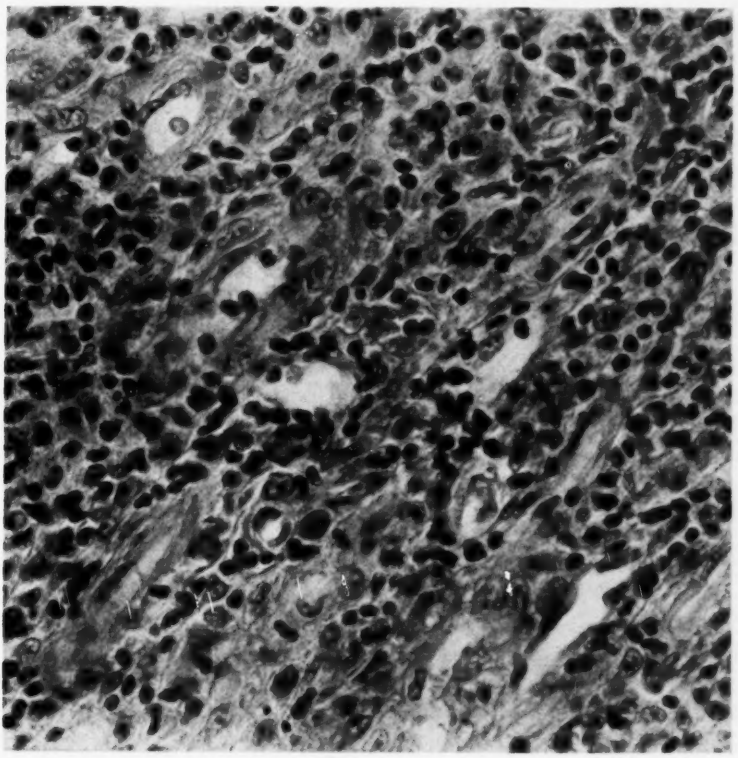

Fig. 3 (Case 2).—High-power view showing many newly formed capillaries surrounded by an infiltrate predominantly of round cells, endothelial cells, and a few of other types.

## PATHOLOGIC OBSERVATIONS

The pathologic changes in the three specimens studied were strikingly uniform in the general character of the tissue reaction to the infection. The lesions were all well developed and corresponded in general to the pathologic picture as it is described by most writers. There were no early lesions among them; therefore, the early pathologic changes are not described. The conspicuous features were marked parakeratosis, acanthosis of a characteristic type, and a sharply marginated intense inflammatory reaction about new-formed capillaries of the upper cutis (Fig. 2).

In the specimen from the second case there was a thick parakeratotic crust containing only a moderate number of leucocytes. Just beneath the parakeratotic layer was a flattened vesicle without much fluid, but with many polymorphonuclear leucocytes in the space. There was a very characteristic downward extension of thin rete pegs, not a true acanthosis, deep into the dense infiltrate in the cutis. One of the most striking changes in the cutis was the new-formed (Fig. 3) capillaries, which were numerous and were surrounded by an infiltrate made up chiefly of round cells, so as to make a confluent infiltrate extending up to and even invading the basal-cell layer in some places. There were, in addition to the predominant round cells, many cells of endothelial type, a few mast cells, and eosinophiles, but surprisingly few polymorphonuclear cells. Beyond the solid infiltrate was a marked perivascular infiltration of the same type. The section in the third case was about the same except for the great amount of edema in the subcutis, greatly dilated capillaries in some places, and thrombosis in many of the capillaries of the upper cutis. The section from Case 1 was similar except that the upper dermis showed fluid-containing areas in which there were lymphocytes; apparently these areas were greatly dilated lymphatics. In none of the sections stained by the Giemsa method were any structures suggestive of inclusion bodies seen.

## THE CAUSE

The causative virus has not been, in our opinion, isolated or studied in animals, and Becker adequately discusses the older theories of the causative virus as reported in the literature. The most complete and convincing study of the virus made in recent years was that by Hester, Boley, and Graham, who investigated an epidemic of natural cowpox which had been present in a herd of 300 dairy cows for several years, with 27 active cases at the time of study. They were unable to transmit the disease to other cattle by vaccinating ground-up infective material on the caudal fold in 34 cattle, ranging in age from calves a few weeks old to bulls several years old; this series included 10 cattle from a farm on which there had never been cowpox. Later all these animals were successfully vaccinated with commercial vaccinia virus. In another group these workers successfully vaccinated with vaccinia virus 33 of 38 cows, and among the successfully vaccinated were 2 who had active lesions of natural cowpox. Subsequently 22 of these 38 animals developed natural cowpox. The authors were unable to grow the virus on the chorioallantois of chicken embryos, and the eggs inoculated hatched normal chicks; however, they were able to grow vaccinia virus on incubated eggs with ease. Their findings indicate that in the cow natural cowpox does not produce immunity to vaccinia virus, nor does vaccination with vaccinia virus prevent subsequent infection with the virus of natural cowpox. They concluded that there was no antigenic relation between vaccinia virus and the virus of natural cowpox, and they could not demonstrate the virus of the latter disease.

Other less extensive virus studies have been done, and in most instances no virus was found on animal inoculation, particularly in the rabbit's cornea. In studies on two of his cases Becker instilled an emulsion of biopsy material into the scarified corneas of rabbits and also injected the material into guinea pigs with no resultant infection. He reviewed the older literature extensively. There are several reports in the literature of positive virus studies in which animal inoculation gave rise to

appearances similar to those produced by vaccinia virus, but most of them are of questionable authenticity. Schultze and associates [12] apparently were able to transmit the infection to other animals, which were then immune to vaccinia virus vaccine, but their results are so at variance with those of others that it must be presumed that in some way their material was contaminated with vaccinia. Salken [13] reported milkers' nodules in six women who had had smallpox in their childhood. He was unsuccessful in his inoculation of eight persons, five of whom had had milkers' nodules, and also in that of a cow and a calf, but he successfully inoculated guinea pigs and after three passages obtained a vaccinia-like virus from their epidemic. However, it seems to us that the disease, which the six women acquired chiefly from sheep in a slaughterhouse, may well have been a vaccinia virus pox of sheep.[14]

## VIROLOGICAL STUDIES

Portions of the specimens removed in Cases 1 and 2 were ground to a fine suspension with a sterile mortar and pestle, using sterile powdered glass. Small amounts of hormone broth were added, a portion at a time as the grinding was done, to make a thin paste. The mixture was lightly centrifuged, and the supernatant fluid was used in subsequent virus studies. Each specimen was divided in equal parts. To one part was added penicillin to obtain a final concentration of 100 units per milliliter, but no antibiotic was added to the other.

Eleven-day-old embryonated chicken eggs were inoculated on the chorioallantoic membrane, in the chorioallantoic sac, and in the amniotic and yolk sacs. The embryos were incubated at 37 C. for five days. Three embryonic passages were made in all, after which the membranes were harvested. They were floated on saline solution and examined for lesions by transmitted and reflected light. They were then ground to a 10% suspension and centrifuged, and the supernatant fluid was tested for hemagglutinin activity.

In addition to the embryos, rabbits and mice were also inoculated. The rabbits were inoculated intradermally after the hair had been removed by clipping. Inoculation following corneal abrasion was also tried. Mice were injected intracranially, intranasally, intradermally, and intra-abdominally. All animals were examined daily for three weeks.

Attempts to isolate the causative agent by the above methods were uniformly negative with one exception. One group of mice inoculated intracranially with nodular material from Case 2 showed signs of restlessness and hyperactivity. This occurred after 48 hours' incubation, and the symptoms resembled those of herpes simplex infection. So closely did the signs mimic herpes that the mice were spun by their tails in an attempt to provoke convulsions. The mice went through motions suggesting that they would convulse, but they did not. The following day they were on their way to recovery. Consequently the mice were killed; their brains were

12. Schultze, W.; Seifried, O., and Schaaf, J.: Die Melkerknoten und ihre Aetiologie, Ztschr. Infektionskr., par. Krankh. u. Hyg. d. Haustiere **31**:295 (Sept.) 1927.

13. Salkan, P. M.: Zur Klinik der Epidemiologie und Ätiologie der Melkerknoten, Acta dermat.-venereol. **14**:342 (Nov.) 1933.

14. Stark, A. M.; Tiesenhausen, M. M.; Gozanskaja, N. M.; Skrozky, E. W., and Schtschastny, D. S.: Über die Pockenätiologie der sog. Melkerknoten, Arch. Dermat. u. Syph. **170**:38, 1934.

removed, ground to a 10% suspension in saline solution, and passed to a second group of mice. The second group exhibited no signs of infection, although observed for three weeks. Since no antibiotics had been employed intracranially, having been administered intra-abdominally (penicillin and streptomycin), the signs observed in the first group may have been due to toxicity.

Immunologic studies using the patients' sera contributed little toward determination of the causative agent. The neutralizing capacity of these sera for vaccinia and herpes viruses was unimpressive. Since late convalescent serum specimens were unobtainable, the immunologic studies could not be considered conclusive.

In summary, attempts to demonstrate the causative agent of milkers' nodules or antibodies against the agent yielded negative results.

## CONCLUSIONS

Natural cowpox in milch cows is common in Iowa and probably throughout the United States. Milkers' nodules, a fairly distinct clinical entity in those who milk infected cows, is caused by the natural cowpox virus, but the infection in man must be rare even though 10 cases were seen in this series.

The virus was not isolated by us, nor has it been isolated in recent years, even though there has been great improvement in the techniques of virus study. The reports in the older literature of isolation of the virus are equivocal.

The virus causing milkers' nodules is not that causing vaccinia, but vaccinia originating from recently vaccinated persons does produce a disease of the teats and udders of cows which is transmissible to human beings, in whom it causes a pock-like eruption, not nodules.

## ABSTRACT OF DISCUSSION

Dr. D. M. Pillsbury, Philadelphia: This very clear and concise discussion by Dr. Nomland and Dr. McKee needs little elaboration. Milkers' nodules is a rather satisfying disease because if one has the opportunity of seeing it once future cases will be recognized immediately. Dr. Nomland has described the clinical and microscopic characteristics clearly. My only qualification for discussing this condition is the fact that my colleagues and I have seen two cases in the last two years. When I saw the first patient, I realized that the condition was something different and that it was an entity, but I must admit I didn't know exactly what it was.

We went through the usual routine of putting down 15 diagnostic possibilities, which did not include milkers' nodules. We then did the usual bacteriological and virological studies, and all these gave negative results. This condition is a demonstration of the importance of morphologic dermatology at times, because one can recognize this disease clearly on the basis of clinical findings. To one who is surrounded by a number of basic scientists it is particularly satisfying to see an occasional clinical condition in which one can say, "I don't think you can prove I am wrong this time."

There are one or two specific points in Dr. Nomland's paper on which I should like to comment. The veterinarians refer to this condition as natural cowpox, as distinguished from genuine cowpox or vaccinia. I hope that the term "natural cowpox" does not get into medical literature too extensively, because it will prove confusing, I am sure. There is no difficulty in differentiating milkers' nodules from vaccinia on the basis of biopsies.

The virus causation of this condition has not been proved in terms of demonstration of the virus. However, the evidence for a virus causation is strong, and I feel sure that the virus will be demonstrated when a sufficient number of cases are seen where facilities for complete virological studies are available. The fact that one is unable to grow the virus on embryonated

eggs is, of course, no particular proof that a virus is not present, since that is the case with warts and chickenpox. Dr. Nomland's paper is an excellent report on a condition which has clear-cut pathognomonic clinical features.

DR. L. H. WINER, Beverly Hills, Calif.: In line with Dr. Pillsbury's comment about the failure to grow the virus from verrucae on embryonated eggs, Lloyd, Macdonald, and Glover (*Lancet* **1**:720-721, 1951) reported a case in which they were unable to grow the orf virus in egg. They stated that cowpox virus produced a typical lesion on the chorioallantois, whereas the virus of orf did not grow. Apparently some viruses have this cultural characteristic in common.

DR. C. GUY LANE, Boston: I wish to add another case of milkers' nodules to this study, inasmuch as this case was lost in the literature in 1940. A case of milkers' nodules was among a group of industrial cases I reported on at the annual meeting of the Ohio State Medical Society (*Ohio M. J.* **36**:937-944 [Sept.] 1940). A man, 48 years old, came into the clinic at the Massachusetts General Hospital, Boston, with a rather unusual appearance which none of us recognized. His story was that he had started milking cows two days before the onset. This gives a little indication of the short incubation period. He did not come to the clinic until two weeks later.

The lesions had started as small eruptions on the symmetrical terminal parts of two forefingers. They gradually increased in size, and in 9 or 10 days they were about the size of those shown in Dr. Nomland's photographs. They became crusted; there was only a slight tenderness of the axillary gland, and the culture showed only the usual staphylococci. It was a most unusual appearance, but I was able to find similar cases in the literature and made a diagnosis of occupational dermatosis, milkers' nodules. Thus, it seems necessary to look for this disease in the East as well as in the Middle West.

DR. WILEY M. SAMS, Miami, Fla.: It may be that milkers' nodules are commoner than we suspect. There is scarcely a community in the country which does not support one or more dairy herds. The disorder is not confined to the Midwest. Fortified by the opportunity of examining the excellent illustrations and slides which Dr. Fred Becker, of Duluth, prepared from his cases, and with my clinical acumen sharpened by reading over the program for our meeting, I was pleasantly surprised to have a patient consult me with a lesion showing the clinical characteristics of a milkers' nodule. The appearance of the lesion was such that diagnoses of ordinary verruca vulgaris and pyogenic granuloma were considered, while the patient's occupation afforded a clue which suggested the more uncommon lesion described as a milkers' nodule. While specific occupational diseases are not too numerous, our changing and advancing technology continues to present new hazards. My patient was a mechanic by profession; but, being unable to obtain such employment, he accepted an unskilled job with a dairy. With no previous experience in milking cows, he was assigned to this occupation. His work consisted in preparing the udders and teats for the application of milking machines. They were washed first with soap and water, and then with a chlorinated disinfectant solution. The occupational exposures and contacts are, of course, the same as those of a milker with a small dairy herd. My patient had not been long employed when the lesion appeared on his wrist, and he reported that some of the cows had small "sores" on the udder.

DR. R. L. SUTTON JR., Kansas City, Mo.: Dr. Pillsbury's comment that the disease is clinically a satisfying entity is certainly appropriate. It is not so satisfying, however, to an inquisitive biologist. One wonders how the disease is transmitted from cow to cow. Has the disease been seen on parts of the body other than the udder? Has it been recognized in the male animal? Has it been transmitted from man to man? I have not seen that. Is there a seasonal incidence? It seems to me that, if so, there is preference for the summer and fall. Has it occurred in several members of one family, all of whom milked the same cows? I have not seen that. It is a disease that a Kansas City dermatologist sees two or three times a year. As for treatment, it appears to me that the disease is not influenced by anything I have done, although, histologically, the structure suggests that x-ray therapy might influence it, but I am not sure that it does. One of Dr. Nomland's patients, whose lesion was in the early vesicular stage and was incised, showed healing promptly. Clinically, the presence of sometimes rather painful lymphadenitis may be noted. In dealing with the patient, you have to reassure him.

DR. S. ROTHMAN, Chicago: Have inoculations ever been done with human material? Does this disease leave immunity in cows and in man?

DR. M. B. SULZBERGER, New York: My colleagues and I saw quite a few cases of this disease in Switzerland, but I haven't seen any since I have been in New York. I probably missed them. In our cases abroad we neglected to do dark-field examinations for treponemes and spirilla. Does anyone know whether such dark-field examinations have been done?

DR. RUBEN NOMLAND, Iowa City: I am grateful to Dr. Pillsbury for his general confirmation of the work we did on milkers' nodules, but we did not add anything new. I think that the disease is always acquired through the milking of infected cows, and the epidemiology is such that the virus must be carried from cow to cow by the milker, though the milker may not necessarily have milkers' nodules. The disease does not occur in beef cattle or in bulls and is probably not transmitted from person to person, but in two instances there was a history of more than one person acquiring the disease from milking the same cow. Immunity in the cow is probably almost complete, but the veterinarians tell me that they see recurrent or relapsing attacks in the same animal.

Briefly, this is an interesting disease syndrome with a very definite course, so that once it has been seen it will never be forgotten. In all probability the virus will soon be found because none of the virus studies, including ours, has dealt with the disease in cows, presumably the best source of fresh virus material.

# PARAPSORIASIS: ITS TREATMENT WITH CALCIFEROL

## Review of Eighteen Cases

ORLANDO CANIZARES, M.D.
NEW YORK

CHRONICITY in spite of treatment is a characteristic of all varieties of parapsoriasis. Therefore, any method of therapy which may favorably alter its chronic course is worthy of trial.

In September, 1948, in the dermatologic service of the late Dr. J. Gardner Hopkins at the Veterans Administration Hospital, Bronx, N. Y., my colleagues and I saw a patient with parapsoriasis of the guttate type, who, after exposure to Florida sunlight, made a complete recovery but had a relapse on his return to New York. Because of this experience, it was thought that vitamin $D_2$ therapy might be of value in this disease. This patient and another, successfully treated with calciferol, were presented at a meeting of the Manhattan Dermatologic Society on Feb. 8, 1949. Descriptions of these two patients and two additional ones were published in a preliminary report.[1]

Prior to our observations and independently of them, Barber and Erskine[2] and Yorke[3] reported to the Royal Society of Medicine on two patients who had parapsoriasis en plaques successfully treated with vitamin $D_2$, which relapsed when treatment was discontinued. About the same time, Goldberg[4] presented a patient with parapsoriasis en plaques at the meeting of the Central States Dermatological Association. This patient had received four months of calciferol therapy without improvement. Subsequently, Goldberg treated two more patients having parapsoriasis en plaques with vitamin $D_2$ also without success.

I recognize the severe handicap in evaluation of a method of treatment of the dermatoses classed as parapsoriasis. They are diseases with rather ill-defined clinical pictures and even more debatable histologic structure.

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Read at the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

From the Section of Dermatology and Syphilology of the Medical Service of the Veterans Administration Hospital, Bronx, N. Y.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the results of his own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Canizares, O.; Dwinelle, J. H., and Shatin, H.: The Treatment of Parapsoriasis with Vitamin $D_2$, J. Invest. Dermat. **16**:121 (March) 1951.

2. Barber, H. W., and Erskine, D.: Parapsoriasis en Plaques Treated with Calciferol, Brit. J. Dermat. **61**:100 (March) 1949.

3. Yorke, A.: Parapsoriasis en Plaques Treated with Vitamin $D_2$, Brit. J. Dermat. **61**:100 (March) 1949.

4. Goldberg, L. C.: Personal communication to the author.

In this paper I present a review of the results obtained in treatment of these diseases with vitamin $D_2$ in 5 personal patients and in 13 patients of several of my colleagues. I also review the possible mechanism of action of this vitamin in parapsoriasis and a possible relationship of this disease to tuberculosis.

## DIAGNOSTIC CRITERIA

I have followed the diagnostic criteria established by McCarthy.[5] I feel that we can be sure of only two types of parapsoriasis, the guttate or papular type and the "en plaque" or patchy type. Pityriasis lichenoides et varioliformis acuta, I believe as Gross [6] did, represents a form of guttate parapsoriasis. I have not seen any case which could be classified definitely as parapsoriasis lichenoides of Brocq, parakeratosis variegata of Unna, Santi, or Pollitzer, or lichen variegatus of the early English and American writers. Only one of our patients had lesions with a suggestion of retiform elements, but since the great majority of lesions were typical of the guttate variety the case was classified as such. A similar patient was reported on by Pierard.[7] In the guttate type the lesions are pinhead- to pea-sized papules, round or oval, and a clear red. The larger lesions are paler and flat; the smaller may be slightly acuminate. There may be little scaling. Often the scales are thicker in the center than at the periphery. In our patients the lesions usually were distributed on the trunk, arms, and thighs. Hands, feet, face, and neck were invariably free. In most of the patients the lesions were of long standing and gave rise to no subjective symptoms. Most patients had received previous topical applications without improvement. The diagnosis of the varioliform type was made when typical vesicular, bullous, hemorrhagic, or even necrotic lesions were seen. In one of our patients the lesions in one attack were of the varioliform type, later relapsing to the guttate type. Lesions began as rounded, yellow to brown papules which often presented small vesicles at the summits. They spread rapidly. Hemorrhagic and necrotic lesions were followed by scarring. In one patient lesions of the guttate type appeared after the acute process had subsided. Usually lesions in different stages occurred simultaneously. General symptoms, such as mild fever, generalized adenopathy, and malaise, were often noted.

The patients with parapsoriasis en plaques presented the typical yellow to rosy, rounded or oval plaques located on the trunk or extremities. In some instances lesions ran parallel to the long axis of the extremities or ribs. The borders were rather well defined but faded into the surrounding normal skin. The surface was smooth or slightly scaly, and there was no infiltration.

In most instances the clinical diagnosis was corroborated by the microscopic study. It is not within the scope of this paper to discuss the histologic features of this disease. Most observers agree that a typical picture does not exist. McCarthy [5] stated that the entire histopathologic picture is a most uncharacteristic one, simply representing a moderate degree of chronic inflammation involving the upper layers

5. McCarthy, L.: Differential Diagnosis of Parapsoriasis, Arch. Dermat. & Syph. **45**:81 (Jan.) 1942.

6. Gross, P.: Pityriasis Lichenoides et Varioliformis Acuta (A Variety of Parapsoriasis), Arch. Dermat. & Syph. **23**:33 (Jan.) 1931.

7. Pierard, J.: Sur une forme atypique de parapsoriasis en gouttes: Rapports du parapsoriasis en gouttes et de la parakeratosis variegata, Arch. belges dermat. et syph. **3**:198 (Feb.) 1947.

of the skin. This is true especially in the "en plaque" variety. Weidman [8] pointed out that in a great majority of cases the histopathologist can state only that the picture is compatible with a diagnosis of parapsoriasis. The microscopic examination is of value in ruling out other conditions with a more specific histologic picture, such as psoriasis, mycosis fungoides, and the tuberculids. In the cases of this series the designation "compatible with parapsoriasis" was considered confirmatory of the clinical diagnosis.

### CLINICAL COURSE

In order properly to evaluate treatment in a cutaneous disease, it is necessary to have an understanding of the behavior of the untreated disease.

Most dermatologists agree that parapsoriasis is notoriously chronic. This is so important to many authors that they consider it one of the essential features. Likewise, its resistance to treatment, local and systemic, is well known. The multiplicity of treatments advocated is evidence that none of them is particularly effective.

In the guttate type remissions and exacerbations are not uncommon. McCarthy [5] stated that in certain seasons this type may disappear spontaneously. Dwinelle [9] saw a patient with typical parapsoriasis guttata, who, a few years later, without treatment, showed no trace of the disease. Montgomery [10] followed 8 of 24 patients with the guttate type and noticed complete involution in 4.

Pityriasis lichenoides et varioliformis acuta, a subvariety of the guttate type, may pursue an acute course of a few weeks to several months. In some instances there may be recurrences for several years. In Montgomery's series there was a patient, aged 69, who had had recurrent attacks of parapsoriasis for 35 years.

Parapsoriasis en plaques, according to Ormsby,[11] is extremely persistent, with practically no tendency to spontaneous involution. However, in 5 of 20 cases of this type, Montgomery [10] obtained a history of remission each spring or summer. He believed that exposure to sun accounts for these seasonal remissions. In one of his patients the eruption disappeared completely and two years later had not recurred.

All these remissions were gradual and spontaneous and should not be confused with recovery following a short period of medication.

### RELATION OF PARAPSORIASIS TO TUBERCULOSIS

The effect of vitamin $D_2$ in parapsoriasis may be interpreted as evidence in favor of the tuberculous causation of this disease. The possible tuberculous origin of parapsoriasis was first suggested by Civatte [12] in 1906. More recently, however, he stated that the tuberculous causative factor has not been proved histologically, bacteriologically, or immunologically.[13] Several authors, Civatte, Gougerot, and

8. Weidman, F. D., in discussion on McCarthy.[5]

9. Dwinelle, H.: Personal communication to the author.

10. Montgomery, H., and Burkhart, R. J.: Parapsoriasis: Its Relation to Mycosis Fungoides and Tuberculosis; A Review of 52 Cases, Arch. Dermat. & Syph. **46**:673 (Nov.) 1942.

11. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 326.

12. Civatte, A.: Note pour servir à l'etude des tuberculides papulosquameuses: trois cas de tuberculides a forme de parapsoriasis, Ann. dermat. et syph. **37**:209, 1906.

13. Civatte, A.: Les parapsoriasis, in Darier, J.; Sabouraud, R.; Gougerot, H.; Milian, G.; Pautrier, L. M.; Ravaut, P.; Sézary, A., and Simon, C.: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, Vol. 7, p. 686.

Combes,[14] have reported on patients cured with injections of gold preparations. Ravaut [15] cited one case of parapsoriasis en plaques in which the tuberculous causation was proved with reasonable certainty. Milian and Pinard [16] reported a case of guttate parapsoriasis with telangiectatic and purpuric lesions. Histologically this case was of a tuberculous nature. These cases probably belong to a group which Montgomery designated "lichenoid tuberculid."

In the five personal cases of this series there was no previous individual or familial history of tuberculosis.

### RELATION TO ULTRAVIOLET IRRADIATION

For a long time ultraviolet irradiation has been advocated in the treatment of parapsoriasis. Almkvist, Touton, and Klausner in Europe and Wise, Schamberg, and Andrews [17] in this country were among those who have obtained improvement with this therapy in the guttate and "en plaque" varieties. Andrews [17] stated that intensive doses are necessary.

Ehrmann [18] combined heliotherapy with arsenic administration, since he felt the latter increased capillary sensitivity to light. He used sodium cacodylate preceding and concomitantly with the ultraviolet irradiation and believed that a severe erythema was essential for satisfactory results. Dryer [18] tried to sensitize his patients to light with injections of trypaflavine* (acriflavine U. S. P.).

The distribution of the eruption in parapsoriasis also may be evidence of the effect of sunlight. The parts of the skin conventionally exposed to light, the face, neck, and hands, are almost invariably free of eruption.

It is known that provitamin D in human skin is activated into vitamin D through the effect of ultraviolet irradiation. Provitamin D is probably eleidin, a sterol secreted by the sebaceous glands and more closely related to cholesterol than to ergosterol. There is no evidence that activation ever takes place in the body by other means than ultraviolet irradiation. Storage of provitamin D must be relatively small, since it is impossible to activate any large amount by exposure of the body to ultraviolet irradiation. The effect of calciferol in parapsoriasis may indicate that the improvement which has often followed ultraviolet irradiation is due to activation of provitamin D with its subsequent conversion.

### MECHANISM OF ACTION OF VITAMIN $D_2$

In a study of calciferol therapy in patients with cutaneous tuberculosis, Michelson [19] stated that he knew of no satisfactory explanation for its effectiveness. A similar statement may be made of this medicament in respect to parapsoriasis. The healing in the patients of this series resulted in apparently normal or slightly hyper-

14. Combes, F. C.: Personal communication to the author.

15. Ravaut, P.: Cited by Civatte.[13]

16. Milian, G., and Pinard, M.: Parapsoriasis en gouttes, sa nature tuberculeuse, Ann. dermat. et syph. **38**:477, 1907.

17. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1939, p. 216.

18. Cited by Juliusberg, F.: Die Parapsoriasis, in Handbuch der Haut- und Geschlechtskrankheiten, edited by J. Jadassohn, Berlin, Springer-Verlag, 1928, Vol. 7, Pt. 1, p. 288.

19. Michelson, H. E.: Calciferol in the Treatment of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **58**:680 (Dec.) 1948.

pigmented skin, as is to be expected in a superficial dermatosis. No scarring was noticed; consequently, the hypothesis offered by Michelson, that increased oxygen consumption of the individual cells leads to scar formation in cutaneous tuberculosis treated with calciferol, could not be applied in the case of parapsoriasis.

The response of parapsoriasis to calciferol may be explained on the basis of its possible tuberculous causation. The action of this drug in cutaneous tuberculosis is well established, and there is almost unanimous agreement that its use constitutes a definite advance in the treatment of lupus vulgaris. However, in the tuberculids, and in some hematogenous types, results have been on the whole somewhat disappointing. Michelson [19] reported lack of success in papulonecrotic tuberculid, rosacea-like tuberculid, and erythema induratum. Since the tuberculous causation of parapsoriasis is far from being proved, the mode of action of calciferol in this disease is probably different from that in cutaneous tuberculosis.

Stokstad and Jukes [20] pointed out that there seems to be a relation between vitamin D and sex hormones, although vitamin D has no estrogenic activity. Androgens are slightly rachitogenic, whereas estrogens are antirachitic. Apparently vitamin D is also an aphrodisiac; but neither this nor the estrogenic effects, both of which are seen occasionally after its administration, have ever been associated with intoxication. According to Dowling,[21] calciferol may act as a catalyst. There is substantial evidence that in rickets vitamin D acts by stimulating the parathyroid glands. Whether its action in other diseases is similar has not been determined. Weld [22] has shown that in normal adults moderate doses of vitamin D promptly improve capillary resistance, acting even more effectively than ascorbic acid.

Knowledge of the relation between vitamin $D_2$ and other vitamins and hormones is still in its infancy, and until more data are available it is impossible to understand completely the mechanism of its action.

## TOXICITY

Calciferol is potentially toxic. A series of 77 patients treated by Pascher and co-workers [23] showed the most toxic symptoms to be nausea, abdominal pain, vomiting, frequency of urination, thirst, fatigue, and weakness. Severe and even fatal intoxication may be produced by excessive amounts. A question could be raised concerning the advisability of using a drug which is potentially toxic in treatment of diseases that do not endanger the general health of the patient. In my opinion calciferol can be used safely with proper clinical and laboratory supervision. In this series kidney irritation with albumin, hyaline, and granular casts developed in only one patient. This gradually subsided within two months. It has been stated by Reed, Struck, and Steck [24] that the severity of toxic reactions

20. Stokstad, E. L. P., and Jukes, T. H.: Water Soluble Vitamins, Ann. Rev. Biochem. **18**:435, 1949.

21. Dowling, G. B.: Vitamin D in the Treatment of Cutaneous Tuberculosis, Brit. J. Dermat. **60**:127 (April) 1948.

22. Weld, C. B.: A Capillary Resistance Test and Its Relation to Vitamins C and D, J. Pediat. **9**:226, 1936.

23. Pascher, F.; Silverberg, M. G.; Marks, I. E., and Markel, J.: Therapeutic Essays of the New York Skin and Cancer Unit, Post Graduate Medical School, New York University, Bellevue Medical Center: Essay II: Calciferol ($D_2$), J. Invest. Dermat. **13**:89, 1949.

24. Reed, C. I.; Struck, H. C., and Steck, I. E.: Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations, Chicago, University of Chicago Press, 1939, p. 207.

may be conditioned by dosage per unit of body weight, duration of administration, age, individual susceptibility, preexisting pathologic changes, functional state of the endocrine system, and other factors. The keeping of these ideas in mind in the selection of the patient and the dosage of calciferol will reduce the incidence of toxicity.

At the onset of this investigation, weekly laboratory studies to detect preclinical evidence of toxicity were made. These included complete urinalyses, blood counts, determinations of sedimentation rates and blood calcium and phosphorus levels, and roentgenograms of the bones. Later, we did only urinalyses and blood calcium evaluations, with questioning of the patients about subjective symptoms of toxicity.

## REPORT OF CASES

Eighteen patients with parapsoriasis were treated. There were six women, eight men, and four children, their ages ranging from 2 to 65 years. The duration of the disease varied from two months to 10 years. The cases of the varioliform variety were of shorter duration. The longest duration was in cases of the "en plaque" type. The follow-up period varied. Some patients were seen eight or eleven months after treatment had been discontinued.

Five of the patients were under my personal care; the others were treated by my colleagues. No local treatment was given to my patients; they were hospitalized and kept under close super-

*Result of Treatment of Parapsoriasis with Vitamin D*

| | | |
|---|---|---|
| Total number of patients treated | | 18 |
| Parapsoriasis guttata | | 6 cured |
| | (10 patients) | 2 controlled while receiving therapy |
| | | 2 failures |
| Pityriasis lichenoides et varioliformis acuta | | 3 cured |
| | (3 patients) | |
| Parapsoriasis en plaques | | 2 cured |
| | (5 patients) | 1 improved |
| | | 2 failures |

vision. The rest of the patients were ambulatory and usually were seen once a week, but at times less frequently. Ultraviolet radiation was given to five. On one patient boric acid ointment was used.

There were 10 patients with the guttate type. The first patient received 150,000 units of calciferol daily for four weeks. The second patient received the same dosage for two weeks, and then the amount was reduced to 100,000 units daily for another two weeks. The third patient received 50,000 units daily for two weeks with improvement but after a relapse was given 100,000 units daily for four months. The fourth patient received 500,000 units a week for two months. In these four patients there was complete recovery after a period of treatment which varied from four weeks to four months. The fifth patient received 50,000 units daily for four months. The disease was controlled while under therapy but relapsed when medication was discontinued.

In one patient with parapsoriasis guttata some of the lesions presented a vague retiform configuration. This patient received three courses of four weeks each of 150,000 units of calciferol daily. Each course resulted in complete remission, only to be followed by relapse within two or three weeks.

The four children of this series presented lesions of the guttate type. Two of them, aged 6 and 4½ years, received 50,000 units daily for three months and six weeks, respectively. Both were clinically cured. The two youngest, aged 2 and 3½ years, received doses of 30,000 and 20,000 units, respectively, daily for one month without benefit.

There were three patients with pityriasis lichenoides et varioliformis acuta of Mucha-Habermann. In the first patient, in one attack all varioliform and necrotic lesions disappeared after administration of 150,000 units of calciferol daily for three weeks. Two months later a typical guttate parapsoriasis developed which also subsided with the same medication. He

was seen eight months later and was still free of lesions. The second patient at the onset also presented a varioliform eruption, but later typical guttate lesions developed. Treatment was started with 50,000 units of calciferol daily for four weeks, and then 100,000 units was given for two weeks. Medication was discontinued because of urinary signs of toxicity, although the cutaneous lesions had subsided entirely. The third patient received 150,000 units of calciferol daily and generalized ultraviolet irradiation weekly, with complete remission.

Five patients with parapsoriasis en plaques were treated with calciferol. One patient received 150,000 units for three weeks and was discharged clinically cured. Six months later he was still free of lesions. Another patient received 100,000 units daily for three months and was greatly improved. A third patient received 150,000 units daily for six weeks, some ultraviolet irradiation, and 200 r of x-rays to three lesions, with complete remission. Two patients received 100,000 and 150,000 units, respectively, for several months without improvement.

## COMMENT

A study of this series shows that calciferol is definitely beneficial in treatment of parapsoriasis guttata and pityriasis lichenoides et varioliformis acuta. Ten patients with parapsoriasis guttata were treated; six recovered completely within one to four months; two relapsed when medication was discontinued, although one of these remained relatively free of lesions with a daily dosage of 50,000 units.

There were two failures, both in small children who received 30,000 and 20,000 units daily. It is possible that the requirements of calciferol are higher in children, but because of potential toxicity larger doses may not be advisable.

Satisfactory results were obtained in the three patients with pityriasis lichenoides et varioliformis acuta. The results in the "en plaque" type were equivocal; of five patients, two were cured, one improved, and two did not improve. It is difficult to interpret this disparity of results. It may be an argument in favor of the belief that at least some cases of this variety of parapsoriasis are examples of early mycosis fungoides. The answer may be found in prolonged subsequent study and observation. It may indicate also that the cause of parapsoriasis en plaques is dissimilar to that of parapsoriasis guttata.

Ultraviolet irradiation was given to five patients in addition to calciferol. Two of these previously had received irradiation alone without improvement. There was no evidence that the addition of ultraviolet irradiation altered the usual course of the disease in patients receiving it simultaneously with large doses of calciferol.

Best results were obtained in adults when the initial dosage was 150,000 units a day for three or four weeks with subsequent reduction.

## SUMMARY AND CONCLUSIONS

Eighteen patients with parapsoriasis of various types were treated with calciferol. Of 10 patients with the guttate type, 6 made a complete recovery after one to four months of treatment; 2 had remissions while receiving therapy but relapsed when medication was discontinued, and 2 small children failed to respond at all.

Three patients with pityriasis lichenoides et varioliformis acuta, a variety of guttate parapsoriasis, were treated. All responded favorably within six weeks.

Of five patients with parapsoriasis en plaques, two were cured within six weeks, one was improved, and two were unimproved.

It may be stated, therefore, that calciferol has a beneficial effect on parapsoriasis guttata and in pityriasis lichenoides et varioliformis acuta. This effect may be tem-

porary, for relapse may occur when medication is discontinued. The value of calciferol therapy in parapsoriasis en plaques is uncertain.

The best results were obtained with initial doses of 150,000 units daily.

The beneficial effect of ultraviolet exposures in some cases of parapsoriasis may be explained on the basis of activation of cutaneous provitamin D by the radiant energy.

The mechanism of action of calciferol is unknown and should not be construed as a point in favor of the tuberculous origin of this disease.

Dr. Harry Arnold, Dr. David Bloom, Dr. Adrian Brody, Dr. Irving Cohen, Dr. Maurice Costello, Dr. Paul Gross, Dr. Emory Ladany, and Dr. Samuel Peck gave permission for inclusion of their patients in this series.

## ABSTRACT OF DISCUSSION

Dr. M. J. Costello, New York: The observation by Charpy and by Dowling in 1943 that vitamin $D_2$ therapy would arrest, improve, or cure lupus vulgaris was one of the great discoveries of this decade. The application of this therapy to the treatment of parapsoriasis is also an important contribution.

It is possible that failure in some of the cases of parapsoriasis in Dr. Canizares' series was due to the fact that several forms of vitamin $D_2$ were used, whereas, the best results reported in the treatment of lupus vulgaris, at least by Charpy, were with administration of vitamin $D_2$ in alcohol by mouth, supplemented by small doses of calcium, a low-salt diet, milk, and large quantities of vegetables. In my own experience in the treatment of lupus vulgaris it made little difference whether the vitamin $D_2$ was used in ethyl alcohol, propylene glycol, oil or other carriers. An important fact is that intensive vitamin therapy has proved curative at times in diseases not due to vitamin deficiencies.

It is to be remembered that exposure of the skin to sunlight has been effective in treatment of diseases of the skin that are not favorably affected by vitamin $D_2$ therapy, namely, psoriasis and atopic dermatitis. The deduction that vitamin $D_2$ therapy should be effective in diseases of the skin that are favorably influenced by sunlight is not, therefore, a correct one.

Charpy thought that vitamin $D_2$ was effective by virtue of its production of local tissue acidosis and that the aim of treatment was to maintain local tissue acidosis; the other thought cited by Dr. Canizares was that improvement was a consequence of increased oxygen consumption. Dowling suggested that calciferol cannot be regarded as a chemotherapeutic agent for tuberculosis but may be a catalyst or accelerator of a normal process. It is thought that vitamin $D_2$ probably exerts its beneficial effects by enhancing the action of phosphatases in tissues, liberating phosphate ions for metabolic and enzymic reactions.

The first form of vitamin D obtained in crystalline condition was a molecular compound consisting of equal parts of calciferol and lumisterol and was called vitamin $D_1$. When calciferol was obtained in free condition, it was called vitamin $D_2$. It should be noted that the meaning of $D_1$, $D_2$, $D_3$ in this connection is not analogous to $B_1$, $B_2$, $B_3$ as applied to water-soluble vitamins, since the various forms of vitamin D perform the same function in prevention or cure of rickets, while $B_1$, $B_2$, $B_3$ refer to substances which cannot replace one another.

It is unusual that parapsoriasis (a possible tuberculid) should respond favorably to vitamin $D_2$, for in the treatment of tuberculosis of the skin only the true "tuberculoses," such as lupus vulgaris and scrofuloderma, respond well; papulonecrotic tuberculid and erythema induratum do not respond to vitamin $D_2$ therapy.

Certainly, the clinical appearance of the lesions of varioliform type of parapsoriasis is suggestive of the atypical papulonecrotic tuberculid, even though the locations are different, but the similarity ends with the disseminated and symmetrical appearance of the lesions. Seldom does parapsoriasis coexist with tuberculosis elsewhere in the body, nor does pulmonary tuberculosis develop later in the patients suffering from parapsoriasis. The histologic structure of parapsoriasis is not tuberculoid, and there is no hyperergy to tuberculin.

The papulonecrotic tuberculid does not respond to vitamin $D_2$ therapy, while in most cases the varioliform type of parapsoriasis does. However, the response to vitamin $D_2$ therapy of

eruptions thought to be papulonecrotic tuberculid may place them in the classification of parapsoriasis. In my own experience parapsoriasis is a persistent dermatosis notoriously resistant to therapy. This constant feature has helped to differentiate it from guttate psoriasis.

It is difficult to understand why the various forms of parapsoriasis react in such a capricious manner and why the eruption recurs as promptly as therapy with the drug is discontinued. The inconstant therapeutic response to vitamin $D_2$ in parapsoriasis is not unlike the similar behavior of certain dermatoses treated with cortisone.

Treatment with vitamin $D_2$ is not without danger; in one reported case death from hemoptysis occurred during treatment.

Before administering vitamin $D_2$, it would be wise to take roentgenograms of the chest of all patients to rule out the possibility of pulmonary tuberculosis, which may be reactivated by vitamin $D_2$ therapy. Regular blood calcium determinations should be performed. Great care should be exercised in the administration of vitamin $D_2$ to young children because of the danger of mobilization of calcium from normal reservoirs, especially in the osseous system.

It is difficult for a single investigator, even one who has access to a large amount of clinical material, to evaluate a remedy or to observe the actual toxic effects of any given drug in the treatment of a rare disease. I should like to make a plea at this time for the pooling of clinical data, especially with reference to severe tragic toxic manifestations of a drug, and for the immediate dissemination of such information by short reports in current journals.

DR. V. PARDO-CASTELLO, Habana, Cuba: It is hard to understand how such a conglomerate of syndromes as this we call parapsoriasis always responds to treatment with one special drug. Some of these syndromes last a certain time, and then the patient recovers spontaneously without treatment. Parapsoriasis lichenoides et varioliformis acuta lasts four to six weeks, perhaps two or three months, and in my experience, the patient usually recovers.

In the other cases, particularly in the Juliusberg or lichenoid type, I have used consistently as most of us do, ultraviolet rays, vitamin D, and many other drugs, sometimes perhaps for psychological reasons, and seldom have I noted any response. Most patients continue to have their parapsoriasis for months or years and occasionally recover spontaneously. It was, therefore, with great interest that I heard Dr. Canizares' contribution, and I hope we find in vitamin $D_2$ the effective treatment for parapsoriasis.

DR. BRAULIO SÁENZ, Habana, Cuba: We are all aware of the failure of the various treatments used for this stubborn disease, parapsoriasis, and, as the presenter very well points out, no new developments have added any confirmation to the supposed tuberculous causation of parapsoriasis, as advanced by Civatte some 50 years ago.

In regard to the capricious evolution of this disease, I remember a case of the guttata type that I observed in 1924. The patient was treated with gold compounds and was followed for three years. No results were obtained; the condition remained unchanged, and the patient was lost to observation. Twelve years later, I met this patient on a boat. He approached me and said "Dr. Sáenz, when I decided to quit coming to you, I was so discouraged that I gave up all kinds of medicines; to my surprise, some five years later the lesions regressed spontaneously, and I have been well ever since."

Four years ago I saw a woman, aged 20 years, with parapsoriasis en plaques covering almost the entire skin surface, the face included. She had been treated for two years without results. At first sight, the condition closely resembled poikiloderma atrophicans vasculare. Not knowing what to prescribe and considering the predominant vascular aspect of the lesions, I advised low voltage (hot) mercury vapor light and rutin by mouth. Six months later the condition had almost regressed. I have not heard from the patient since.

Recently I saw two patients with Mucha's parapsoriasis varioliformis acuta, one in February of this year. A youth aged 20 years had been treated for four months with vitamins and low voltage mercury vapor light without benefit. I was surprised at the numerous inflammatory elements in which hemorrhages and necrotic lesions were evident, suggesting an increased allergy. Suspecting a possible viral causation, I tried aureomycin therapy. Within 10 days the lesions had changed tremendously, and two weeks later the patient was absolutely free of lesions and has continued to be well.

By coincidence, about 10 days later a member of the staff brought a patient with a similar condition to the hospital. The eruption was not so profuse and was not invading the face. The administration of aureomycin cleared up the condition in 10 days.

Just before I came to this meeting I saw two other patients with parapsoriasis. One was a man with parapsoriasis en plaques brought to the clinic by the same physician who brought in the second patient with parapsoriasis varioliformis. The patient has been treated with vitamin $D_2$ for only 10 days. I do not know the results. The other was a boy, aged 8 years, treated for more than two years for a supposed skin condition due to intestinal allergy and given a restricted diet. The diagnosis of parapsoriasis guttata was not established. With precautions because of his age, he was given vitamin $D_2$. I shall be glad to report to Dr. Canizares on the results of the therapy in these two patients.

Dr. Oscar Gans, Frankfurt, Germany: I think we need not stress that the fact that two diseases respond to the same remedy does not prove that they have the same origin. I should like to emphasize that parapsoriasis variegata, which Unna brought to our attention should not be forgotten. This form of parapsoriasis is very rare; I have seen it only twice in my life, the first case in 1917, and the second only six weeks ago. But I can assure you that if ever you come across such a case you will realize that it is an entity.

Dr. Orlando Canizares, New York: The course of parapsoriasis is discussed in the paper. The spontaneous recovery is a slow process which can easily be differentiated from the rapid recovery that often follows the administration of calciferol.

Dr. Gans mentioned parapsoriasis variegata. I have not seen any patients with this condition.

Recently, I saw a patient with parapsoriasis guttata whom I could not include in this series. His general health was poor, since he was undernourished and a chronic alcoholic. Calciferol and other supportive therapy was administered, but for three weeks the eruption failed to change. When his general health improved, there was a rapid recovery, and in three more weeks the lesions disappeared entirely, leaving only a residual pigmentation.

Parapsoriasis is a rare entity; at the Bronx Veterans Administration Hospital we needed three years to collect five cases, and I could present a larger series today only because of the generosity of my colleagues, to whom I am indebted. Many details of the treatment have yet to be determined, but it is my impression that results obtained justify further use of calciferol in the treatment of the stubborn conditions grouped under the heading parapsoriasis.

# PITYRIASIS RUBRA PILARIS

## Clinical and Laboratory Observations on Combined Treatment with Corticotropin and Vitamin A

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IT IS NOW generally agreed that some disturbance of vitamin A metabolism is important in the causation of pityriasis rubra pilaris.[1] However, knowledge concerning the absorption, conversion, transport, storage, and utilization of this dietary factor is still far from complete, and very little is known of how or why this mechanism is interfered with in patients with pityriasis rubra pilaris.

Two varieties of the disease may be distinguished: first, that in which there are definite indications of vitamin A deficiency, resulting from deficient intake, abnormal demand, or a gross fault in absorption, and which is readily improved by vitamin A therapy, and, second, that in which such gross deficiency cannot be demonstrated and which shows only slow response to ingestion of massive doses of the vitamin over a considerable time. In general, the first variety usually appears for the first time in adult life, while the latter form may and frequently does make its appearance in childhood. In such cases it would appear that somewhere along the line there is a fault in metabolism and the name dysvitaminosis [2] might be more appropriate than either hypovitaminosis or avitaminosis.

O'Leary [3] has suggested that in the latter form there may be a deficiency of some other vitamin or combination necessary to the utilization of vitamin A which

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Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

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1. (*a*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, pp. 342-343. (*b*) Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949, p. 439. (*c*) Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42 (Jan.) 1941. (*d*) Leitner, Z. A., and Ford, E. B.: Vitamin A and Pityriasis Rubra Pilaris, Brit. J. Dermat. **59**:407, 1947. (*e*) Porter, A. D., and Godding, E. W.: Pityriasis Rubra Pilaris and Vitamin A, ibid. **57**:197, 1945. (*f*) Weiner, A. L., and Levin, A. A.: Pityriasis Rubra Pilaris of Familial Type: Experiences in Therapy with Carotene and Vitamin A, Arch. Dermat. & Syph. **48**:288 (Sept.) 1943. (*g*) Jeghers, H.: Skin Changes of Nutritional Origin, New England J. Med. **228**:714, 1943.

2. This name was suggested by Dr. M. B. Sulzberger in discussion on Brunsting and Sheard.[1c]

3. O'Leary, P., in discussion on Cornbleet, T., and Cohen, D.: A Case for Diagnosis (Pityriasis Rubra Pilaris?), Arch. Dermat. & Syph. **47**:463 (March) 1943.

has not as yet been recognized. Spector and associates [4] stated that a defect in the ability of the intestinal mucosa to absorb vitamin A and fat is due to the lack of some extrinsic substance which may be vitamin B, and Gross [5] has demonstrated improvement on treatment with vitamin B. Others [6] have felt that failure of antioxidants (vitamin E?) to prevent destruction of the vitamin in the intestine or the liver may be a factor. At least 15 instances of familial occurrence in the same and succeeding generations have been recorded. Sulzberger, in discussion on the paper of Brunsting and Sheard,[1c] has suggested that possibly nevoid anomalies result in faulty utilization of dietary ingredients.

Although it would be the most reliable manner of assessing vitamin A metabolism, there is at present no satisfactory way of directly measuring the vitamin A content of the liver in human beings, since needle biopsy is considered hazardous. However, as Ruch and co-authors [7] point out, the amount present in blood serum at intervals after ingestion of large doses may be an index of that which has been "pushed out" of the liver. Therefore, blood levels after such ingestion are a rough indication of liver content, since a liver with low content would remove more from the circulating blood than would one which was, so to speak, saturated. Thus, so-called absorption curves may be an index not only of the efficiency of this nutritional factor but also of the state of liver storage, and their significance in demonstrating a fault in metabolism is greater than that of simple blood vitamin A levels, which tend to remain within normal range until gross depletion of the depot in the liver has taken place.

The mechanism of utilization of vitamin A by the skin is not known. We can say only that, under normal conditions, the presence of vitamin A in adequate amounts appears to prevent abnormal keratin formation and, possibly secondary to this, to allow normal function of sebaceous glands. In this connection, Cornbleet and Popper [8] in their report on fluorescence microscopy observed characteristic vitamin A fluorescence in subcutaneous fat but not in the epidermis or epidermal lipids, even after ingestion of large amounts of the vitamin. It, therefore, appears that either the control of keratinization by vitamin A is exerted from a distance or, if the control is exerted locally, the vitamin is destroyed or changed so that it does not produce fluorescence.

In cases in which a simple deficiency due to inadequate intake, abnormal demand, or faulty absorption of fats could be excluded, a dysvitaminosis A must indicate a fault in absorption, conversion, storage, transport, or utilization. Until we have a more complete understanding of these processes, it is difficult to assess them or to suspect which one or ones are at fault. However, one might assume

4. Spector, S.; McKhann, C. F., and Meserve, E. R.: Effects of Disease on Nutrition, Am. J. Dis. Child. **66**:376 (Oct.) 1943.

5. Gross, P.: Pityriasis Rubra Pilaris and Vitamin Therapy, Arch. Dermat. & Syph. **44**:270 (Aug.) 1941.

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that study of absorption or tolerance curves in a sufficient number of cases in which dysvitaminosis is suspected would throw some light on the efficiency of absorption and/or storage.

Aside from the factor of heredity seen, according to Wright and Niedleman,[9] in about 7.15% of cases, we have no definite knowledge of the reason for a dysvitaminosis A in pityriasis rubra pilaris. In 1938, Goodman [10] propounded the question, "Will a relation be established between pituitary hormones and vitamin A?" Many investigators have felt that endocrine factors were probably involved, and Leitner and Ford [1d] have suggested the possibility that the pituitary-adrenal axis is in some way concerned.

Recently, within a short period we saw two boys with pityriasis rubra pilaris. It was decided to administer corticotropin together with vitamin A to these patients, observing the results from a clinical and histologic standpoint and studying the vitamin A curves during treatment. It was hoped that, with this combination, rapid improvement might be achieved and then maintained by continuing therapy with the vitamin alone.

## METHOD OF INVESTIGATION

The two patients, after preliminary investigation had indicated the functional integrity of the adrenal cortex and failed to reveal evidence of liver damage, any definite endocrinopathy, or faulty absorption or utilization of fats, received 15 mg. of corticotropin,[11] four times a day for 20 days. In order not to confuse the picture, no local treatment, other than very slight lubrication of the palms and soles with petrolatum at long intervals, was used during the period of this report. During the first 14 days, the patients were on a regular hospital diet without supplemental vitamins, but on the 15th day the administration of vitamin A in the dosage of 50,000 U. S. P. units (oil concentrate) three times a day was begun. For six days, therefore, the vitamin preparation and corticotropin were administered concomitantly, after which administration of the vitamin A alone in the same dosage was continued for the 67 days covered by this report. During the 20 days of administration of corticotropin, five biopsies were performed, the specimens in all instances being taken from clinically typical nutmeg-grater-like patches on the knees.

Determination of fasting blood levels of vitamin A, as well as of absorption curves, was made before the institution of corticotropin therapy, three times during the period of administration of the hormone, and one month after the use of corticotropin was stopped. The second and third determinations during the corticotropin therapy were made, respectively, three and six days after the ingestion of supplemental vitamin A was begun.

The vitamin A determinations were made according to the technique given by Clausen and McCoord,[12] utilizing the Carr-Price blue reaction formed by vitamin A with antimony trichloride. In the analyses reported here an Evelyn photoelectric colorimeter was used with selective filters. Correction was made for the blue color produced by carotenoids in the Carr-Price reaction. Results are reported as 620 units per 100 cc. of serum (relating to spectral transmission of the color at 620 mμ). The same method was used in studies of vitamin A in infants and children by May and associates,[13] who also reported their results in 620 units. The method

9. Wright, C. S., and Niedleman, M. L.: Pityriasis Rubra Pilaris (Acute Type) Responding to Vitamin A Therapy, Urol. & Cutan. Rev. **51**:684, 1947.

10. Goodman, H.: Dermatologic Symptoms of Vitamin Deficiencies, Arch. Dermat. & Syph. **38**:389 (Sept.) 1938.

11. The corticotropin was of bovine origin and was supplied by The Armour Laboratories, Chicago 9.

12. Clausen, S. W., and McCoord, A. B.: The Carotenoids and Vitamin A of the Blood, J. Pediat. **13**:635, 1938.

13. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

of determination and reporting used in this study and that of May and his associates has been in use at Children's Memorial Hospital in Chicago for many years, principally in connection with studies of celiac disease. It was, therefore, felt that, for the sake of comparison with values obtained on other patients with this method there was nothing to be gained by the laborious procedure of calibrating the colorimeter so that results could be expressed in international or U. S. P. units. Furthermore, unless such calibration were done with the use of the same vitamin A standard as was employed by other investigators, the results could not be used for comparison. Determinations at Children's Memorial Hospital of fasting blood levels of vitamin A in infants or children who did not have clinical evidence of vitamin A deficiency, or a disorder that would suggest altered impairment of fat absorption and metabolism, have run from 14 to 32 units over a period of 10 years. May and his co-workers report a variation in 63 normal infants and children of 5.5 to 27.3 units.

In this investigation fasting levels were determined, after which the patients were given 0.1 cc. of percomorph liver oil per pound (0.5 kg.) of body weight,[14] and levels were again determined three and five hours later. Using this technique in 16 normal children, May and his co-authors found the maximum rise in a five-hour postingestion period to range from 22.8 to 198.3 units, with the average being 112.7 units. At Children's Memorial Hospital comparable figures have been obtained, with the result that over the years members of the staff there have come to view anything under a 30-unit maximum rise by this technique as a distinct deviation from normal.

Biopsies were performed repeatedly during the first 21 days of the treatment, so that clinical changes might be correlated with changes in the microscopic picture. It is worthy of mention that although six biopsies were done on each patient there was never any disturbance in healing of the wounds.

## REPORT OF CASES

Case 1.—J. S., a 6-year-old white boy, was one of 10 children in a family of low income. He had had no previous skin disease or "allergy." There was no history of similar eruption in the family. Immediately prior to Jan. 1, 1951, he had mumps without orchitis, making an uneventful recovery in about 10 days.

About Jan. 10, 1951, a thickening of the skin of the palms with exfoliation suddenly developed, leaving the fingers very sensitive and swollen. There was subsequent redevelopment of a thickened keratotic surface. Seven days later, the same process appeared on the soles, with fissuring and marked pain on walking. Along with this, a "scaliness" manifested itself on the chest, abdomen, face, and ears. There was no itching, and there had been no history of unusual contact or any internal medication.

General physical examination revealed a well-developed, slightly thin white boy, 6 years of age, weighing 48½ lb. (22 kg.), with no significant findings other than those relating to the skin. The eyes, including the eyegrounds, were normal. Examination of the body surface revealed the following:

1. There was marked thickening of the skin of the palms and soles with deep-seated rather dark red color, over which the superficial layers were distinctly yellow. The surfaces were hard and rough, and there was some irregular exfoliation (Fig. 1). There were numerous deep fissures, particularly on the feet.

2. On the knees and elbows were fairly well-defined yellowish-red areas of irregular thickening of the skin with definite follicular exaggeration, producing a nutmeg-grater-like surface.

3. There was moderate red-yellow scaling of seborrheic-dermatitis-like character involving the eyebrows, forehead, and scalp.

4. There were scattered follicular pinhead-sized papules on the extremities, without any particular emphasis on the proximal phalanges of the fingers.

*Laboratory Data.*—Blood studies revealed a hemoglobin concentration of 10.8 gm. per 100 cc. Red blood cells numbered 3,900,000 and white blood cells 6,750 per cubic millimeter, with 47

14. This is equivalent to approximately 6,000 U. S. P. units of vitamin A per pound (0.5 kg.) of body weight.

polymorphonuclear neutrophiles, 44 lymphocytes, 7 eosinophiles, and 2 monocytes per 100 cells. Examination of feces on two occasions revealed no abnormal fat content. The blood Kahn test and the Mantoux test gave negative reactions. Results of urinalysis were normal. Total plasma proteins measured 6.9 gm. per 100 cc., with 4.3 gm. of albumin and 2.6 gm. of globulin. The cephalin flocculation was 1 +. The prothrombin time was 23 seconds (control, 21 seconds). Cholesterol measured 113 mg. and nonprotein nitrogen 25 mg. per 100 cc. Fasting levels of vitamin A were 17 and 15 620 units per 100 cc. of serum. The vitamin A absorption curve showed 16 units on fasting, 28 units at three hours, and 19 units at five hours, a total rise of 12 units.

*Results of Microscopic Examination.*—Biopsy was performed in the prepatellar region. Sections stained with hematoxylin and eosin revealed slight acanthosis, marked hyperkeratosis with patchy parakeratosis, chiefly perifollicular in distribution, and marked follicular plugging. There were slight superficial vascular dilatation and a clumped perivascular round-cell infiltrate

Fig. 1 (Case 1).—Palms before treatment.

composed chiefly of lymphocytes (Fig. 2). Elastic and connective tissue stains revealed no significant abnormalities.

The diagnosis on clinical grounds was pityriasis rubra pilaris, and the histologic observations were entirely consistent with such a diagnosis. It is worthy of note that there were no findings indicative of endocrine abnormality or hepatic lesions. This patient had had mumps shortly before the onset of the skin disease, and the resultant vitamin A demand, together with the fact that possibly previous vitamin A intake had not been large, might have constituted the precipitating cause for the pityriasis rubra pilaris. However, adequate intake of vitamin A did not bring about any clinical improvement in three weeks. The vitamin A levels after three weeks of such intake were at the lower limits of normal, but the absorption curve was abnormally flat.

Case 2.—P. L., a 10-year-old white boy, was said to have had "infantile eczema" that disappeared at 1½ years of age, after which he remained free of any skin disease until the age of 8 years. He then began to have a patchy eruption on the dorsa of the wrists and extensor

surfaces of the legs. This was diagnosed as "eczema," and the patient was investigated from an allergic standpoint with positive results on scratch tests with several foods and inhalants. He was treated symptomatically on this basis, but the eruption did not respond.

On Jan. 17, 1951, he was seen in the outpatient department, and a diagnosis of pityriasis rubra pilaris was made. It was subsequently learned that the same diagnosis had been made by Dr. Ormsby and Dr. Ebert in October, 1950. Treatment was started with vitamin A, 50,000

Fig. 2 (Case 1).—Section from knee before treatment. Hematoxylin and eosin stain; × 72.3.

U. S. P. units three times a day, at the time of the January visit, but in two weeks there had been no improvement, and he was hospitalized on Jan. 31.

He had had mumps in 1945, measles in 1946, and chicken pox in 1947. There had been no illness prior to the onset of the skin eruption, which had developed two years before his admission. There was no history of similar skin disease in the family.

General physical examination revealed a well-developed, well-nourished white boy, 10 years of age, weighing 86¼ (39.1 kg.). There were no significant findings except those relative to

the skin which are given below. The eyes and eyegrounds were normal. The skin findings comprised (1) slight diffuse scaling of the scalp; (2) diffuse yellowish-red thickening of the palms and soles and some grouped follicular keratoses on the dorsa of the hands; (3) thickened patches with a rough horny surface and red-yellow color on the knees, elbows, and anterior surfaces of the ankles (Fig. 3), and (4) slight thickening and irregularity of the nails on the second, third, and fourth fingers of the right hand and the second finger of the left hand. There was slight paronychial thickening about the nails. A culture was made from the nails and was reported by the state laboratory as showing an unidentifiable yeast organism.

*Laboratory Data.*—On blood studies the hemoglobin concentration was 12.4 gm. per 100 cc. There were 4,250,000 red blood cells and 6,750 white blood cells per cubic millimeter, with a differential count of 56 polymorphonuclear neutrophiles, 40 lymphocytes, 2 eosinophiles, and 4 monocytes, per 100 cells. Examination of feces on two occasions revealed no abnormal fat

Fig. 3 (Case 2).—Knees before treatment.

content. The blood Eagle test and the Mantoux test gave negative reactions. Plasma proteins totaled 5.7 gm. per 100 cc., with 3.2 gm. of albumin and 2.5 gm. of globulin. The cephalin-flocculation test gave a negative reaction. The prothrombin time was 23 seconds (control, 21 seconds). Cholesterol measured 272 mg. and nonprotein nitrogen 31 mg. per 100 cc. The vitamin A absorption curve showed 20 units on fasting, 96 units at three hours, and 105 units at five hours, with a total rise of 85 units.

*Results of Microscopic Examination.*—Biopsy was performed in the prepatellar region. Sections stained with hematoxylin and eosin revealed moderate acanthosis, marked hyperkeratosis with a suggestion of follicular plugging, and perifollicular parakeratosis. There was a moderate perivascular round-cell infiltrate in the upper corium composed chiefly of lymphocytes with some plasma cells (Fig. 4). Stains for elastic tissue showed some fragmentation in the areas of perivascular cell infiltrate. Connective tissue stain showed no abnormalities.

The clinical diagnosis was pityriasis rubra pilaris, and the histologic observations were consistent with this diagnosis. The patient had received massive doses of vitamin A by mouth

for two weeks without any improvement, but both his fasting blood level and his vitamin A absorption curves were normal. He seemed to be in normal health, except for the skin disease, and general laboratory findings were within normal limits. In this case there was no suggestion of an abnormal demand preceding the onset of the pityriasis rubra pilaris.

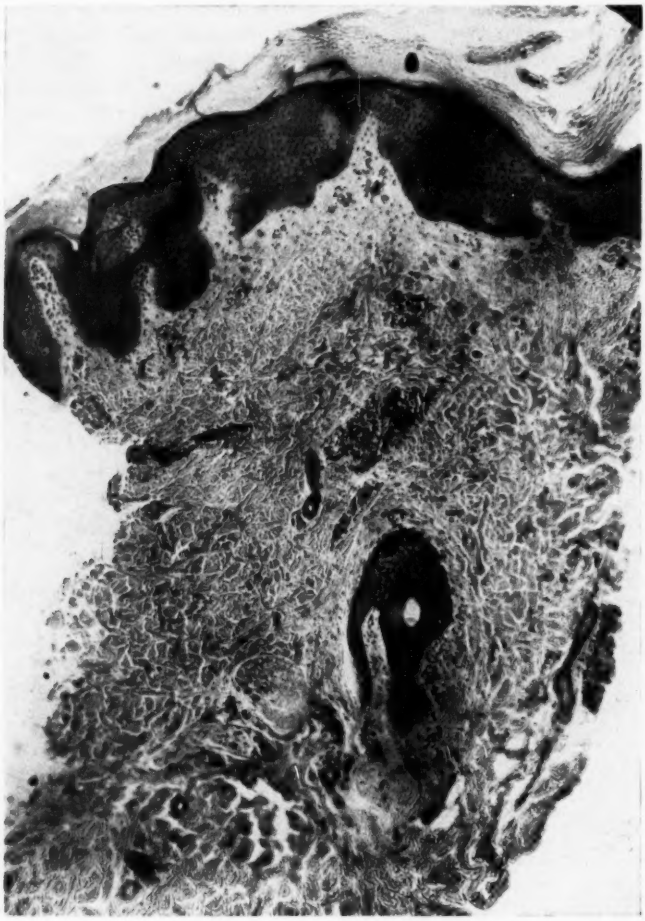

Fig. 4 (Case 2).—Section from knee before treatment. Hematoxylin and eosin stain; × 81.6.

## COMMENT

The treatment, clinical course, vitamin A curves, and microscopic observations in the two cases are summarized in Tables 1 and 2. It is an obvious fact that no valid conclusions can be drawn on the basis of two cases. Nevertheless, observations supporting the effectiveness of the treatment used and indicating the desirability of further investigation along similar and related lines may be considered permissible. With this reservation in mind, a few points are noted.

CLINICAL OBSERVATIONS

From the clinical point of view both patients, one with the severe disease and one whose disease was rather mild, exhibited a striking clinical improvement estimated as 30 to 50% during the initial five days of therapy with corticotropin alone. After this, in spite of continued use of corticotropin for 10 more days, there was only slight further improvement until the oral administration of vitamin A was begun.

TABLE 1.—*Summary of Pertinent Clinical and Laboratory Data in Case 1.*

| | Day of Treatment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5th | 9th | 12th | 15th | 17th | 18th | 20th | 21st | 51st | 82d |
| Corticotropin, 15 mg. q. 6 hr.... | ■ | ■ | ■ | | | | | | | |
| Vitamin A, 50,000 units t.i.d. ..... | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Clinical course .... | 30-40% impvt. | ..... | 45% impvt. | About same | ..... | About same | ..... | 75% impvt. | 90% impvt. | Deterioration to 75% |
| Vitamin A fasting level (initially low normal) | ..... | Low normal | ..... | ..... | Above normal | ..... | Above normal | ..... | Low normal | ..... |
| Vitamin A curve (initially flat) | ..... | Normal | ..... | ..... | Flat | ..... | Barely normal | ..... | Normal | ..... |
| Microscopic observations | * | ..... | * | * | ..... | * | ..... | * | ..... | ..... |

* Asterisks denote days on which biopsies were performed. Microscopic picture showed quantitative improvement only. There were no basic qualitative changes. Findings at all times were consistent with a diagnosis of pityriasis rubra pilaris.

TABLE 2.—*Summary of Pertinent Clinical and Laboratory Data in Case 2.*

| | Day of Treatment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5th | 9th | 12th | 15th | 17th | 18th | 20th | 21st | 51st | 82d |
| Corticotropin, 15 mg. q. 6 hr.... | ■ | ■ | ■ | | | | | | | |
| Vitamin A, 50,000 units t.i.d. ..... | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Clinical course .... | 40-50% impvt. | ..... | 60% impvt. | About same | ..... | 75% impvt. | ..... | 80% impvt. | 100% impvt. | Deterioration to 90% impvt. |
| Vitamin A fasting level (initially normal) | ..... | Low | ..... | ..... | High | ..... | High | ..... | Normal | ..... |
| Vitamin A curve (initially high) | ..... | Flat | ..... | ..... | Very high | ..... | Very high | ..... | Flat | ..... |
| Microscopic observations | * | ..... | * | * | ..... | * | ..... | * | ..... | ..... |

* Asterisks denote days on which biopsies were performed. The microscopic picture, consistent with diagnosis of pityriasis rubra pilaris, showed only quantitative changes during the treatment period. There were no basic qualitative changes.

In the following six days, during which the two preparations were used concomitantly, there was again a striking improvement, so that 20 days after the beginning of this combined therapy improvement was as much as 75 to 90% (Figs. 5 and 6). After one month more of administration of vitamin A alone, the skin of one patient appeared to be normal and that of the other was 90% improved. However, one month later there were slight signs of recurrence. This would appear to represent a more rapid initial response than has been observed in comparable patients treated with vitamin A alone, especially in those with marked clinical manifestations.

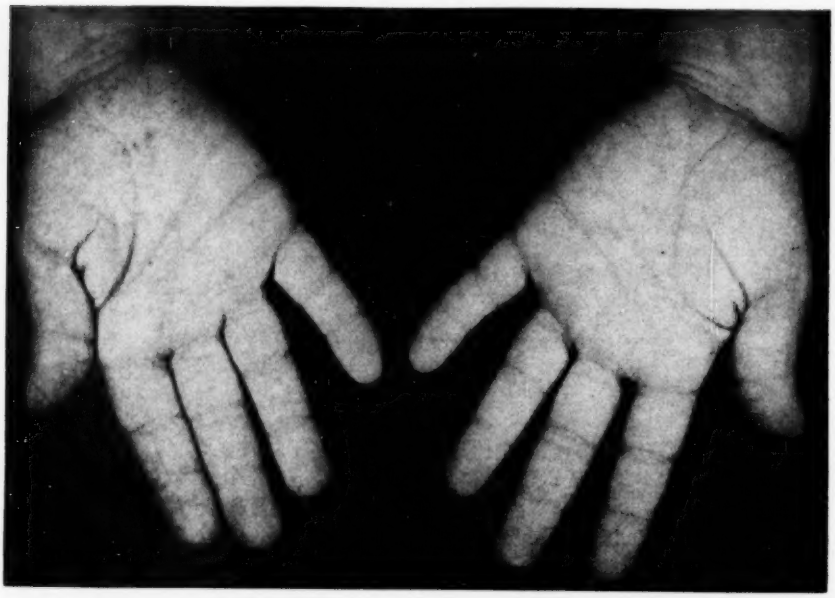

Fig. 5 (Case 1).—Palms after treatment for 20 days.

Fig. 6 (Case 2).—Knees after treatment for 20 days.

MICROSCOPIC OBSERVATIONS

In striking contrast to the clinical behavior, the histologic improvement was slight and of purely quantitative rather than qualitative nature. When clinical improvement was as much as 90%, the picture of hyperkeratosis with patchy parakeratosis and tendency to follicular plugging was still present, though of slightly

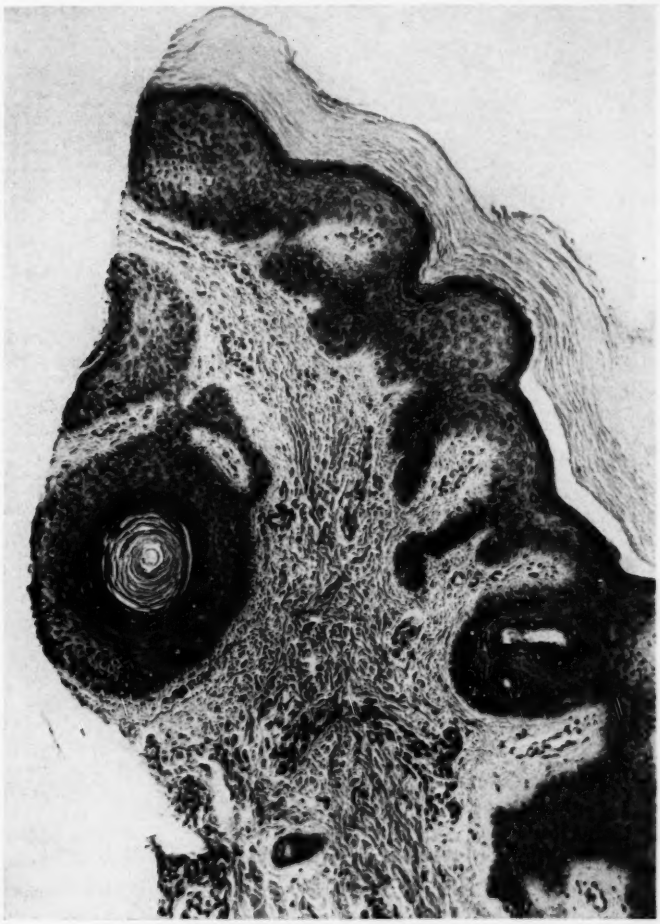

Fig. 7 (Case 1).—Section from knee after treatment for 20 days. Hematoxylin and eosin stain; × 165.2.

less degree, and the stratum corneum was much less compact (Figs. 7 and 8). The only definite changes were a subsidence of the inflammatory reaction in the corium and a slightly increased pigment content in the sections from the later biopsy specimens. No reports were found in the literature relating to serial biopsies in this disease during treatment with vitamin A. However, analogous situations have been noted in which there was a lack of correlation between clinical and histologic change

in other cutaneous diseases under treatment with corticotropin. This substantiates what has been repeatedly observed in regard to the temporary nature of the effect of corticotropin in all but self-limited disorders.

Fig. 8 (Case 2).—Section from knee after treatment for 20 days. Hematoxylin and eosin stain; × 136.7.

### OBSERVATIONS ON VITAMIN A LEVELS AND CURVES

Periodic vitamin A absorption curve determinations gave results, in units, as follows:

Case 1 (Initially Flat)

| | 9th Day | 17th Day | 20th Day | 51st Day |
|---|---|---|---|---|
| Fasting | 15 | 39 | 40 | 18 |
| 3 hr. | 27 | 50 | 47 | 60 |
| 5 hr. | 60 | 64 | 72 | 45 |
| Total rise | 45 | 25 (flat) | 32 | 42 |

Case 2 (Initially Normal)

| | 9th Day | 17th Day | 20th Day | 51st Day |
|---|---|---|---|---|
| Fasting | 13 | 58 | 55 | 23 |
| 3 hr. | 21 | 100 | 100 | 40 |
| 5 hr. | 28 | 250 | 290 | 30 |
| Total rise | 15 (flat) | 192 | 235 | 17 (flat) |

Ruch and his co-workers [7] found tolerance curves to be within normal limits in their two cases of pityriasis rubra pilaris. Apparently, however, they reported the results of only a single curve determination. In each of the cases reported here, two curves of the five determined were flat as compared with normal curves. Moreover, all but one of the curves showing normal values were made during a time that large doses of vitamin A were being administered. This may well be taken as further confirmation of the opinion held by many that some fault of vitamin A metabolism is concerned in pityriasis rubra pilaris and may also suggest the desirability of multiple curve determinations in such investigations. However, no definite light has been thrown on the specific nature of the dysvitaminosis concerned, although it might be considered that faulty absorption or storage has been suggested.

There was no definite conformity pointing to any effect exerted on vitamin A metabolism by administration of corticotropin. In one case the curve rose, and in the other it became markedly flattened after administration of corticotropin alone. Thus, there is no evidence that the hormone either brought about mobilization of the vitamin from storage depots or facilitated the absorption or conversion when the patients were on an average diet. It is true that in both cases the curve rose after a period of the concomitant use of the hormone and the vitamin, and that in one case the curve became flattened after discontinuance of the corticotropin therapy in spite of continued ingestion of the vitamin in large doses. Further investigation on these and additional cases appears to be indicated, but no pattern is apparent here.

If there is no evidence that corticotropin therapy improved absorption, conversion, or storage of vitamin A, how are we to explain the marked initial improvement in these cases after the administration of the hormone for five days and the fact that combined treatment brought about more rapid *restitutio ad integrum* than has been observed in the past with the vitamin therapy alone?

Corticotropin and cortisone are known to suppress symptoms in several types of cutaneous disease, but the mechanism of this physiologic stimulus is not clear. In pityriasis rubra pilaris we are dealing with increased epidermal activity in keratin formation. Apparently vitamin A suppresses such increased activity. Might corticotropin also accomplish this and thus possibly exert an action synergistic with that of the vitamin?

In this connection, the recent work of Castor and Baker [15] may be suggestive. These workers applied cortisone and corticotropin locally to the skin of rats over long periods and compared the treated areas with untreated ones in the same animals. They found that there was a decrease in size of epidermal cells if sufficiently large doses were used for a long enough time and that with still longer periods of treatment sebaceous glands were reduced in size and hair ceased to grow. Unfortunately, no observations were reported on the stratum corneum; however, this work does suggest a depressant action on epidermal-cell activity analogous to that which they observed in the dermis of their rats and which has been observed clinically with systemic administration of these substances to human beings in regard to wound healing.

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15. Castor, C. W., and Baker, B. L.: Local Action of Adrenocortical Steroids on Epidermis and Connective Tissue of Skin, Endocrinology **47**:234, 1950.

## CONCLUSIONS

The administration of corticotropin in conjunction with vitamin A in two cases of pityriasis rubra pilaris was followed by prompt and striking improvement. This improvement is felt to be more rapid though probably not more permanent than that commonly achieved by use of the vitamin alone.

The striking character and rapidity of this improvement seem to justify the use of properly controlled combined therapy for patients with severe pityriasis rubra pilaris if there is no contraindication to the use of the hormone.

Until more is known of the direct effects of corticotropin on the skin and of the manner in which vitamin A is utilized in preservation of normal keratinization by the epidermis, no completely satisfactory explanation can be advanced for the notable improvement following combined therapy.

Serial biopsies performed during a period that marked improvement was being manifested clinically failed to show a parallel improvement in the microscopic picture. The changes in the latter were quantitative rather than qualitative.

Repeated determinations of vitamin A absorption or tolerance curves in these two patients with pityriasis rubra pilaris appear to lend confirmation to the idea that a disturbance of vitamin A metabolism may be important in the causation of this disorder. The manner in which the metabolism is disturbed is not known, but observations reported here suggest that the disturbance is in absorption or storage of the vitamin.

No evidence of an improvement of absorption, conversion, or storage of vitamin A as a result of administration of corticotropin was noted.

There is much that is still unknown regarding vitamin A metabolism in human beings. Furthermore, investigations of blood levels in the past, of which there are many, have not been reported in comparable manner. It would appear that investigation of many more cases of pityriasis rubra pilaris and other cutaneous disorders in which metabolism of vitamin A may be concerned is indicated. Until a satisfactory manner of assessing liver content is available, the repeated determination of vitamin A tolerance curves seems to be the best method, and with a large number of cases so investigated a pattern might become apparent.

## ABSTRACT OF DISCUSSION

Dr. M. J. Reuter, Milwaukee: Perhaps most dermatologists have accepted as an established fact the relation between deficient utilization of vitamin A and pityriasis rubra pilaris. However, results of laboratory investigations utilized in the past to indicate vitamin A deficiency in pityriasis rubra pilaris have been somewhat conflicting, and there has been no conclusive correlation of dark-adaptation tests, blood vitamin A levels, and the therapeutic value of vitamin A. Dr. Webster has given us a complete review of present knowledge of vitamin A metabolism and has been the first to report on multiple blood vitamin A absorption curves in the study of this disease. He has been very conservative in the interpretation of his results, which he feels only appear to lend confirmation to the idea of a disturbance of vitamin A metabolism.

There is evidence that some of the so-called signs of vitamin A deficiency are not specific and are not alleviated by vitamin A supplementation. Because man has such large stores of vitamin A in his liver, it has been difficult to produce experimentally clinical evidence of deficiency, and as a result studies to determine the minimal requirements have been few. One such study is worthy of emphasis.

By maintaining a normal subject on a vitamin A-deficient diet for 598 days, producing a significant fall in blood vitamin A level from 133 to 76 I.U., Hartzler found that the administration of 2,000 to 3,500 I. U. of vitamin A per day was sufficient to stabilize the plasma level or

raise it slightly. Thus, it seems that the massive doses of vitamin A necessary to produce improvement in pityriasis rubra pilaris can hardly be designated a vitamin supplementation effect. I wonder if it could not be called a pharmacologic effect of excess? An analogous situation exists in regard to the pharmacologic use of massive doses of vitamin $D_2$ in the therapy of lupus vulgaris.

Since laboratory investigations regarding the metabolism of vitamin A often give normal results, since vitamin A therapy does not completely cure the disease, and since spontaneous cure does occur, we must be careful not to accept a disturbance of vitamin A metabolism as the sole etiological factor. Unanswered, however, is the question of a possibility of dysfunction in intermediary metabolism of vitamin A, in end-organ acceptance, or in the ability of the skin to utilize the vitamin. Studies made in an attempt to show some underlying metabolic fault, such as in fat or liver metabolism, have been relatively fruitless. Perhaps investigations of the future may show an antivitamin or some other interference with the metabolism of this vitamin. Whatever the underlying factor or factors involved in pityriasis rubra pilaris, it is a reversible process, because, as Kierland and Kulwin have shown, many patients, especially those with the adult type of pityriasis rubra pilaris, ultimately become free of lesions or much improved with a variety of treatments.

Dr. Webster is to be congratulated on his intensive histologic study of serial biopsy specimens of his patients undergoing therapy in this disease. However, in regard to the histologic observations, it should be pointed out that, whereas in pityriasis rubra pilaris there are pronounced epidermal changes with striking follicular hyperkeratosis, other pathologic changes typical of induced vitamin A deficiency in man are absent.

In Dr. Webster's experiment the administration of corticotropin was followed by marked initial improvement, but with the addition of vitamin A to therapy there was rapid clinical improvement in the skin that was felt to be more rapid than that obtained in the past with vitamin A treatment. One can only conjecture about the ultimate outcome with corticotropin therapy alone. A man under my care with pityriasis rubra pilaris appearing in adult life has remained free of lesions for nine months after cortisone therapy. There was no vitamin A added to his usual diet.

As Dr. Webster has stated, at present no adequate explanation can be given for the action of corticotropin in pityriasis rubra pilaris, and one must marvel at its ability to counteract fundamental manifestations of disease. So far little is known of the relation of corticotropin to vitamin A. I am aware of only one other report regarding vitamin A and corticotropin; in this report it was stated that a slight drop in blood vitamin A levels occurred during therapy with the drug.

Dr. A. L. Welsh, Cincinnati: I have recently treated one patient with the combination of biotin, 20 to 40 mg. intramuscularly daily and vitamin A of the water-dispersed type, 300,000 U. S. P. units daily, with complete clearing in approximately seven weeks. This patient was a woman with an extensive eruption, one of the most extensive I have ever seen.

After this experience was related to one of my colleagues, Dr. Lawrence Goldberg, he treated another patient having pityriasis rubra pilaris with the same combination of drugs. His patient was a man of about 50. The patient's eruption cleared in five weeks. I treated a 30-year-old white woman who had this disease with 200,000 U. S. P. units of water-dispersed vitamin A and 800 mg. of synthetic vitamin E daily. Her lesions cleared completely in six weeks.

After hearing Dr. Webster's excellent paper, I thought that while corticotropin seems to further the action of vitamin A in patients who have pityriasis rubra pilaris, the combination of biotin or vitamin E (since they are nontoxic) with the water-dispersed form of vitamin A might offer a safer approach to the treatment of this disease.

Dr. Webster's use of corticotropin as an adjunct to the action of another drug (in this instance, vitamin A) suggests that investigation of combinations of the steroids with other drugs, to enhance their therapeutic action, might reveal some interesting, valuable facts.

Dr. Herbert Rattner, Chicago: I am not sufficiently equipped to discuss the metabolism of vitamin A, but I should like to remark upon Dr. Webster's paper in a general way. Those of you who attended the meeting of the American Academy of Dermatology in Chicago last December will recall Dr. Levine's stirring dissertation on corticotropin and cortisone. At the time he predicted that these steroids would be found wanting as curative agents except in diseases,

such as drug eruptions, in which the etiological factors no longer play a role. He also said these steroids might prove harmful in certain infections, such as tuberculosis; but he did extol them as the best tools for research that have come along in many, many years and said that if they were used properly they should open up a new era in medicine. He made a strong plea that these agents be used properly and not indiscriminately.

It seems to me that Dr. Webster has done just that. He has put a research tool to its proper use. He has attempted with it to help solve a mysterious problem, and for that he is to be complimented.

DR. JAMES R. WEBSTER, Chicago: Dr. Reuter has admirably rounded out the discussion of vitamin A metabolism, bringing in many points that had to be omitted in the condensed presentation. He has emphasized that the undoubted relation of vitamin A to pityriasis rubra pilaris is not to be interpreted in the light of a simple deficiency.

Dr. Rattner has mentioned the underlying philosophy which prompted our use of corticotropin in this preliminary study. It is felt that further investigation is warranted, based on the hypothesis that the ability of the hormone to overcome clinical manifestations of disease is reflected in its effect on the physiology; thus, some definite alteration in metabolism of vitamin A may be brought to light when the various phases of the metabolism have been investigated in a sufficient number of cases. In this connection we are considering further comparison of the effectiveness of oil and water vehicles, as well as the effect on absorption of bile salts and pancreatic extracts, and further studies on the relation of vitamins B and E to the entire problem.

# RETICULOHISTIOCYTOMA OF THE SKIN

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CUTANEOUS nodules are seen frequently in patients suffering from diseases of the joints. In most instances they occur as nodules of rheumatoid arthritis. Less often they are associated with rheumatic fever or gout. The nodular dermatosis that we are reporting bears a gross resemblance to the cutaneous lesions of the above diseases. Histopathologic examination shows that these nodules are unique, however, in being composed of masses of bizarre multinucleated giant cells.

This dermatosis either is rare or has rarely been reported in the past, and the identity of the pathognomonic cells has been variously interpreted in the few cases that have been observed. Allen [1] studied sections from two cases, and he considered the nodules to be reticulohistiocytomas. In Allington's case [2] the diagnoses of ganglioneuroma, histiocytoma, and myoblastoma were considered. Zak [3] reported four cases as reticulohistiocytomas of the skin. In 1932 we prepared and studied sections from multiple lesions of a patient of Dr. W. A. Pusey and Dr. F. E. Senear; we diagnosed the lesions at the time as reticulohistiocytic granuloma or reticuloendothelioma, a diagnosis concurred in by Dr. R. H. Jaffé. This case was later investigated extensively by Montgomery and O'Leary, and it was the basis for their paper, "Multiple Ganglioneuromas of the Skin." [4]

In our present cases we have produced evidence that the cells composing these nodules are of reticuloendothelial origin. The lesions are not true neoplasms, and it would be more correct to use for them the designation of reticuloendothelial granuloma. We believe, however, that confusion may be avoided by retaining the name already established for this entity, reticulohistiocytoma of the skin.

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From the Department of Dermatology and Syphilology, University of Illinois College of Medicine.

Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

1. Allen, A. C.: Survey of Pathologic Studies of Cutaneous Diseases During World War II, Arch. Dermat. & Syph. **57**:19 (Jan.) 1948.

2. Allington, H. V.: A Case for Diagnosis (Ganglioneuroma? Histiocytoma? Myoblastoma?), Arch. Dermat. & Syph. **62**:452 (Sept.) 1950.

3. Zak, F. G.: Reticulohistiocytoma ("Ganglioneuroma") of the Skin, Brit. J. Dermat. **62**:351 (Sept.) 1950.

4. Montgomery, H., and O'Leary, P. A.: Multiple Ganglioneuromas of the Skin, Arch. Dermat. & Syph. **29**:26 (Jan.) 1934.

REPORT OF CASES

CASE 1.—J. R. L., a white man 50 years of age, was employed as a worker in steel mills for several years. In 1943 there was an insidious onset of generalized joint pains and stiffness, diagnosed as rheumatoid arthritis. This has persisted in spite of treatment and has involved chiefly the hands and feet, but to a less extent other joints also, including the spine and jaws. In 1947 the patient first noticed the appearance of soft nodules on the extensor surfaces of the elbows and on the hands. Those on the elbows disappeared spontaneously, but those on the hands persisted and became firm. New lesions appeared on the hands, ears, scalp, forehead, and nose as small shiny papules, but these soon began to grow larger. On the hands the young papules were small and freely movable. After a gradual increase in size, however, they became hard, deep, and more firmly fixed. Once present, all the lesions have persisted throughout the period of our observation of nearly a year, and new lesions have continued to appear up to the present. The evolution of the lesions was not at any time influenced by any form of treatment directed to the rheumatoid arthritis, and treatment included the administration of 1 gm. of aureomycin daily for five weeks. The lesions were at all times free from any subjective symptoms.

Fig. 1 (Case 1).—Nodular lesions on the hands and a ganglion on each wrist.

In its greatest distribution the eruption has involved only the hands and the head. The most fully developed lesions were those on the hands (Fig. 1). On the dorsal surface of all the fingers, both overlying the joints and on the phalanges, there were many split-pea- to hazelnut-sized nodules. These were globular, sharply circumscribed, hard, and only slightly redder than the surrounding skin. The small papules were located superficially in the skin, while the larger ones were subcutaneous and fixed, even though the skin could be moved freely over them. Nodules were present also on the dorsal surface of the hands, on the volar surface of the fingers, and on the palms. Those on the palmar surfaces were fixed to the underlying tissue. On the back of each wrist there was a walnut-sized, soft, fluctuating mass that was apparently a ganglion. On the outer surface of both ears (Fig. 2) there was a mosaic of many pinhead-sized to slightly larger, shiny, flesh-colored papules. A few of the older lesions were larger, and they had recently begun to protrude from the surface of the anthelix. On each side of the nasal septum near the orifice there was a large, firm nodule, and protruding from the columella were several small papules of recent origin. On the scalp, the back of the neck, and the forehead there was a diffuse eruption of pinhead- to pea-sized, shiny, flesh-colored, rounded papules.

Investigation during a long period of observation in the Research and Educational Hospitals, University of Illinois, did not produce much helpful information on the pathogenesis of the

lesions. Aside from the rheumatoid arthritis and the cutaneous lesions, the patient was comparatively well. He was 5 ft. 8 in. (172.7 cm.) tall, weighed 134½ lb. (61 kg.), and had a blood-pressure reading of 110/70. There was no evidence of chest, heart, or intra-abdominal abnormality.

Urinalysis gave normal results. Examination of the blood showed the hemoglobin content to be 15 gm. per 100 cc.; the erythrocytes numbered 5,150,000, and the leucocytes, 7,500 per cubic millimeter, with a differential count of 70% neutrophiles, 4% monocytes, and 26% lymphocytes. The hematocrit reading was 46%, and the sedimentation rate was 7 mm. per hour. The Kahn test of the blood gave a negative reaction. Chemical examination of the blood showed that 100 ml. of serum contained 4.3 mg. of inorganic phosphorus, 10.2 mg. of calcium, 3.1 mg. of uric acid, 145 mg. of cholesterol esters, 5.1 gm. of serum albumin, 1.7 gm. of serum globulin, 6.8 gm. of total serum proteins, and 1.53 gm. of gamma globulin. Examination of a smear of sternal marrow revealed a normal condition. Tests for liver function gave normal results. Electrocardiographic tracings were within normal limits.

Fig. 2 (Case 1).—Many small papules on the ears.

Roentgenologic examination showed a normal cardiac silhouette and normal lung fields. The long bones were normal, and the mineral content of the bones of the hand was satisfactory. The roentgenologist's impression was as follows: "The changes in the hands and feet most likely represent a severe type of gouty arthritis of an unusually marked degree. Other possibilities which must be remotely considered are psoriasis and inactive rheumatoid arthritis. The knees and elbows are involved with minimal osteoarthritis. There is minimal osteoarthritis involving the dorsal spine. There is evidence of degenerative arthritis involving the facet joints of the lumbosacral area."

Biopsies were performed on lesions from the fingers, scalp, ear, and nasal septum, and sections were stained with hematoxylin and eosin, Van Gieson stain, Weigert elastic tissue stain, Perles stain for the Prussian blue reaction, Bodian stain, Sudan III, thionin blue, and toluidine blue.

A section from a small papule on the scalp contained normal hair follicles, sebaceous glands, and sweat glands, and it showed the epidermis to be flattened in one area. Beneath the flattened part of the epidermis there was a small zone in the upper corium that contained many large cells

of ameboid shape. Each cell had a pale grayish-red cytoplasm and one to several large, pale, ovoid or round nuclei, each with a small dark nucleolus. In some cells the nuclei were clumped at one end, in others they were in the central portion, and in a few they were distributed throughout the cell. The cellular infiltrate was not circumscribed, nor were the giant cells closely aggregated. They were rather loosely distributed in this zone, and the individual cells were separated from each other by fibrous connective tissue. The superficial blood vessels were dilated, and they were surrounded by loose mantles of cellular infiltrate containing lymphocytes and small histiocytes. The giant cells were demonstrated more readily in the sections prepared with the Van Gieson stain, which showed that the intervening collagen fibers were stained normally. Staining with Sudan III revealed no definite droplets of fat, but the cytoplasm showed a slightly reddish hue.

A section from a larger papule on the right ear disclosed a more densely packed, subepidermal group of multinucleated giant cells, which were, nevertheless, separated from each other by connective-tissue fibers. The Sudan III stain showed a more reddish hue in the cytoplasm than the previous section. A section from a large nodule on the side of the nasal septum revealed a flattened epidermis, a diffuse cellular infiltrate in the upper corium containing many lymphocytes and a few giant cells, and a large, circumscribed, densely packed mass in the deep corium. This mass was composed of clumps and strands of multinucleated giant cells separated from each other by a dense fibrous connective tissue and a voluminous lymphocytic infiltrate. Sudan III stain showed a definite reddish hue in the giant cells, as if the cytoplasm contained fat in the form of minute droplets.

A large nodule was excised from a finger. In this the epidermis and upper corium were normal. In the deeper part of the corium there was a circumscribed, but not encapsulated, dense, pale-staining mass (Fig. 3*A*). Within this there were many multinucleated giant cells of varying size and shape, lying diffusely in a stroma of densely packed fibrous connective tissue. The Van Gieson stain showed collagen fibers to be present throughout the mass, but with the Weigert stain elastic fibers could not be demonstrated. Above the border of this mass there was a narrow band composed of dilated blood vessels, each having a normal intima and a small mantle of round-cell infiltrate, and many multinucleated giant cells of bizarre shape, lying singly or in strands. The Ziehl-Neelsen stain failed to show any acid-fast micro-organisms in the section, and Perles' Prussian blue reaction was negative for iron. Examination under a polarizing microscope did not demonstrate any doubly refracting particles. No nerve fibrils were found with the Bodian stain, and staining with thionin blue (Fig. 3*B*) and toluidine blue failed to show Nissl granules in the cytoplasm of the giant cells.

A large nodule on the finger was injected with a few minims of a 1% aqueous solution of saccharated iron oxide for vital staining. The nodule was excised 48 hours later, and sections were stained for Perles' Prussian blue reaction. With this stain it was seen that much of the injected iron had been phagocytized by the abundant smaller histiocytes that were present in the infiltrate. Many of the large giant cells also showed fine blue particles in the cytoplasm, which indicated that even these cells had the power to take up injected colloidal iron.

Specimens taken from the nodules and from normal skin were submitted to Dr. Ross C. MacCardle, principal cytologist at the National Cancer Institute, for study by microincineration and histospectrography. His report follows:

"1. *Microincineration.*—The ash of the giant multinucleated cells in the dermis consists chiefly of potassium and sodium, with very little residue of calcium and/or magnesium. There is almost no silicon. Normally there should be large quantities of calcium, magnesium, and silicon in the nucleus and, to some extent, in the cytoplasm. In fact, there is an unusually small amount of silicon in the entire section of this skin, including the epidermis. It is my impression that the small areas of unaffected skin adjacent to the lesion also lack silicon. I cannot conceive of an individual's getting a diet low in silicon in this day and age. However, it may simply be that the skin is unable to retain sufficient quantities of silicon.

"Another striking thing about the giant cells is the large number of very small particles of iron oxide ash throughout the cytoplasm. I have not been able to demonstrate them by Prussian blue stain, because, I presume, the iron exists in such minute particles and is tightly bound as biologically active organic iron. The dermal macrophages are filled with iron particles; however, I believe that this is not important since the particles probably represent iron derived from disorganized blood cells of the lesion. The whole skin seems to be deficient in silicon and calcium

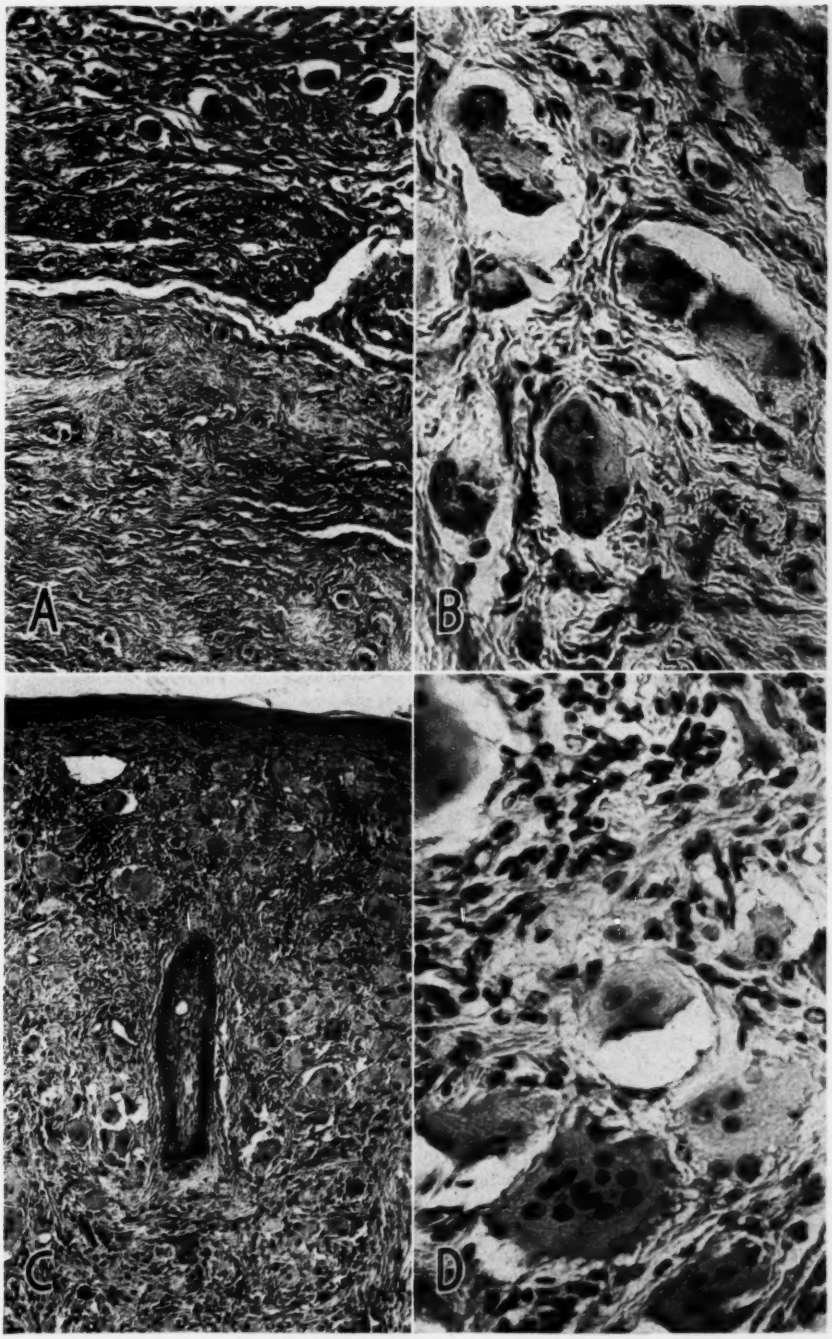


Fig. 3.—*A* (Case 1). Hematoxylin-eosin stain; × 94. Circumscribed dense fibrotic mass in the deep corium containing scattered giant cells. There is an overlying, more vascular zone containing many giant cells. *B* (Case 1). Thionin stain; × 400. Giant cells containing many nuclei but no Nissl granules. *C* (Case 2). Hematoxylin-eosin stain; × 94. Superficial papule, showing many densely packed giant cells, hair follicles, and dilated blood vessels. *D* (Case 2). Hematoxylin-eosin stain; × 400. Ameboid giant cells, containing many pale nuclei with dark nucleoli, and intervening connective tissue.

and/or magnesium. However, this deficiency may simply be the result of the general disturbance which occurs in any hyperactive tissues, and these elements are, of course, of the greatest importance in maintaining a normal state of the skin. It is not very likely that the blood lacks these elements, but it is possible that, as in neurodermatitis, the skin is unable to absorb or retain sufficient quantities of these elements.

"A more important point to me is the large quantity of iron present, undoubtedly, as active or organically bound iron (disregarding the deposits in macrophages). Could it be that the patient has been getting excess quantities of iron in some form? As you know, much of the excess iron is ordinarily stored in the skin. Too much of it may have disturbed the skin. Several years ago I induced formation of giant cells (evidently derived from fibroblasts) by injecting iron into the dermis of rats.

"2. *Histospectrographic Analysis.*—Unfortunately, I can say nothing very specific about the spectrographs. The lines for iron are not very clean because all the important lines coincide with lines for other elements. The silicon line is less intense in the lesion than it is in the unaffected skin specimen which you sent me. I would have suspected this from the incinerated section."

CASE 2.—This patient was studied by Dr. Frederic T. Becker, of Duluth, Minn., and it is with his consent that we include the case in our report.

Mrs. M. G., a 36-year-old white housewife and the mother of four children, has always been well except for periodic hay fever and an uneventful appendectomy in 1938. At the age of 17 years a positive Mantoux reaction was obtained, but periodic chest roentgenograms have all been reported as normal. The present skin eruption began in July, 1949. At this time, she denied any medication except during a month or two of the previous winter, when she had taken 5 or 10 drops of an iodine preparation daily because of goiter. She had noticed increased nervousness.

The general physical examination revealed a well-developed, well-nourished white woman. A funduscopic examination disclosed an essentially normal condition. The eyes, ears, and throat revealed no abnormality. There was no palpable lymphadenopathy. The abdomen revealed a well-healed scar. The spleen and liver were not enlarged. The heart and lungs were normal on physical examination and fluoroscopic study. The blood pressure was 124/82, and the pulse was regular, with a rate of 78. Abdominal and pelvic examination revealed no masses, tenderness, or abnormality. The results of a neurologic examination were essentially normal. There was some swelling of both peripatellar bursae, more marked on the left. There were some thickening and shortening of the volar tendons of the fourth and fifth fingers, bilaterally. Cutaneous examination revealed numerous reddish-yellow papules scattered over the face, the ears, and the forearms, and also on the V of the neck. Situated on the fingers were definite hard nodules which varied in size from that of a pinhead to that of a pea. The areas which were principally involved were the exposed parts of the body. There was no involvement of the lower extremities.

Laboratory examination revealed a blood sugar level of 123 mg. per 100 cc., and a dextrose-tolerance curve was entirely normal. The urine on repeated examinations was normal. Blood cholesterol, cholesterol esters, and total blood lipase were all normal. The sedimentation rate was 9 mm. in one hour. The white blood cell count was 8,300, with a normal differential count of 49 neutrophiles, 45 lymphocytes, 1 monocyte, 4 basophiles, and 1 band cell per 100 cells. Serologic tests of the blood gave negative reactions. Roentgenograms were taken of the entire skeleton, and they were all normal, except for those of the hands, which showed a slight irregularity at the perimeter of most of the interphalangeal joints. This irregularity was bilaterally symmetrical and was accompanied with several small defects in the metaphysial regions. The tuberculin test elicited a positive reaction with a dilution of 1:10,000. Chest roentgenograms, anterior and lateral, revealed no parenchymal abnormality or disturbance of the bony structure of the thoracic cage.

Biopsy specimens were taken from a nodule on the ear, from one on the finger, and from one of the papules on the forearm. Sections were prepared with the same stains as were used in Case 1, and they showed essentially the same characteristics (Fig. 3*C* and *D*). Examination under a polarizing microscope did not disclose any doubly refracting particles, and staining with toluidine blue did not demonstrate any Nissl granules in the cytoplasm of the giant cells. Lipid stains, namely, Sudan III and Nile blue sulfate, did not reveal any definite fatty material, but the Sudan III in some areas stained with a rather dirty yellow appearance.

### DIFFERENTIAL DIAGNOSIS

There are no clinical features that can be helpful in differentiating lesions of reticulohistiocytoma from any other single or multiple persistent cutaneous nodules. In each of the four cases reported by Zak there was but one lesion, and the clinical diagnoses suggested by the gross appearance of the lesion included nevus, fibroma, sebaceous cyst, basal-cell carcinoma, and squamous-cell carcinoma. In cases associated with arthritis, as Allington's case and our Case 1, the diagnoses considered before histopathologic examination were nodules of rheumatoid arthritis, gout, xanthoma, and granuloma annulare. The diagnosis of reticulohistiocytoma, therefore, is largely the problem of the dermatopathologist.

The specific histopathologic diagnosis of a section is suggested at once by the presence of large bizarre-shaped, multinucleated giant cells, with large pale nuclei and dark nucleoli, and the separation of these cells by intervening fibrous connective tissue. To make the identification of these cells more certain, one should employ differential stains, such as Sudan III to demonstrate intracellular fat, Van Gieson stain to show the intervening collagen fibers, Bodian stain to show the absence of nerve fibrils, and thionin blue to show the absence of Nissl granules. Vital staining with colloidal iron is decisive in demonstrating the reticuloendothelial nature of the giant cells.

Of the nodular dermatoses that may be confused with reticulohistiocytoma, all can be differentiated on the basis of histopathologic features.

Nodules of rheumatoid arthritis [5] show a central zone of necrosis of large areas of subcutaneous tissue, bounded by a layer of proliferating cells that are arranged radially and surrounded by a peripheral zone of inflammatory cells. Increasing amounts of connective tissue are formed at the periphery, often resulting in dense fibrous scars, and occasionally there is calcification of the necrotic zone. The pathologic changes here are chiefly necrotic and proliferative.

In nodules of rheumatic fever there is a predominance of inflammatory and exudative changes. The central area contains swollen, hyalinized, and fragmented collagen, a change described as "fibrinoid degeneration." The intermediate zone contains edematous and inflamed connective tissue, with a diffuse distribution of inflammatory cells. The peripheral zone tends to be vascular and to show hyperemia and exudation. The tissue response here suggests that repair takes place more promptly with only slight scarring.

Nodules or tophi of gout are characterized by sharply outlined masses of densely packed crystals of urates surrounded by a mantle of chronic inflammatory cellular infiltrate containing foreign-body giant cells.

Histiocytoma, or nodular subepidermal fibrosis, shows a circumscribed, but not encapsulated, densely packed mass in the upper part of the corium. In this area there are many intertwining strands of cells and connective-tissue fibers. The cells vary greatly in appearance, and they may be large pale histiocytes in some lesions which contain fat and hemosiderin, or small and narrow fibroblasts or connective-tissue cells in lesions that are fibrotic.

Xanthoma may be readily identified by the presence of foam cells and, at times, Touton giant cells, both of which contain fat that stains brilliantly with Sudan III.

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5. Bennett, G. A.; Zeller, J. W., and Bauer, W.: Subcutaneous Nodules of Rheumatoid Arthritis and Rheumatic Fever, Arch. Path. **30**:70 (July) 1940.

Granuloma annulare in a section from a well-developed lesion shows a zone of necrobiosis in the upper corium surrounded by a layer of palisade-like cellular infiltrate containing epithelioid cells, lymphocytes, and connective-tissue cells. Mucin can be demonstrated in the necrotic zone.

Myoblastoma at times bears a great histopathologic resemblance to reticulohistiocytoma. While occasionally the cells may be multinucleated, most of them contain a single pale nucleus. The cytoplasm is pale and granular, and it is not stained by Sudan III. The cells are generally closely aggregated to form a mosaic, without the abundant intervening connective tissue that is seen in reticulohistiocytoma. Pseudoepitheliomatous hyperplasia is a common finding here, while it has not been observed in reticulohistiocytoma.

Ganglioneuroma can be differentiated only by special staining with Bodian stain to show nerve fibrils and with thionin blue to demonstrate Nissl bodies. These are small chromophil granules that are distributed in the entire cytoplasm of the ganglion cells, except in its most peripheral layer and the zone immediately adjacent to the nucleus. If it were not for these differential stains which elicit histopathologic features that apparently are pathognomonic, it would be difficult to differentiate between ganglioneuroma and reticulohistiocytoma.

## SUMMARY AND CONCLUSIONS

Two cases are reported of a rare dermatosis with multiple cutaneous nodules which have unique histopathologic features. The lesion contains many large giant cells of varying shape and size, each containing many nuclei with dark nucleoli. The giant cells occur singly, or they are arranged in strands or dense masses, but in all forms they are separated from each other by fibrous connective tissue.

Staining with Sudan III and vital staining with colloidal iron have produced evidence that these cells are of reticuloendothelial origin. Microincineration of tissue in one case showed that there was almost no silicon but that there was a greatly increased amount of iron present in the giant cells. In view of the patient's former employment in the manufacture of steel, this observation suggests one possible etiological factor in the pathogenesis of these lesions.

The lesions of reticulohistiocytoma are differentiated from those of rheumatoid arthritis, rheumatic fever, gout, histiocytoma, xanthoma, granuloma annulare, myoblastoma, and ganglioneuroma.

## ABSTRACT OF DISCUSSION

Dr. Hamilton Montgomery, Rochester, Minn.: I am in accord with the essayists' use of the term, reticulohistiocytoma cutis, to classify and describe their case and the one of Dr. Frederic Becker which they reported. I believe Dr. Michelson and Dr. Allington and Dr. Templeton have other cases that fall in this group. Another case which belongs in this group is one of Dr. Bedford Shelmire. The patient, a man aged 30, had multiple small pinhead- to pea-sized reddish tumors scattered on the face, arms, and trunk, totaling about 150 in number. On biopsy of the first specimen received in February, 1944, from Dr. Shelmire, and on subsequent biopsies, I suspected ganglioneuroma, but thionin-stained sections were negative for Nissl granules. Dr. A. C. Broders suspected a myoblastoma. Stains for lipids were negative, and in 1946 I tentatively classified this case as one of an unusual type of histiocytoma. I should now call it one of reticulohistiocytoma cutis. The clinical appearance of the lesions in Dr. Shelmire's case was very similar to that of the lesions just shown by Dr. Caro and Dr. Senear, but, unlike other cases of reticulohistiocytoma cutis, the lesions have involuted completely.

I wish to add to the above group of cases that of a woman aged 24 seen by Dr. O'Leary and myself at the Mayo Clinic in May, 1950, because of a generalized eruption involving the scalp, forehead, nose, neck, and arms. There had been swelling of some of the joints, including the fingers, symptoms of fatigue, and bouts of fever. Diagnosis of xanthoma had been made elsewhere from a biopsy specimen of the hand because of the large pale polyhedral cells. Other laboratory tests had given normal results. She had received a low-fat diet, treatment with penicillin, and fever therapy without benefit. When this patient was first seen at the clinic, the preliminary clinical impression was that the condition was some type of lymphoblastoma. Roentgenologic examination revealed some diffusion of fluid in the knee joint and osteoporosis of the right hand and wrist. Other laboratory tests yielded essentially normal results. A specimen taken for biopsy from the right elbow failed to reveal any lipids and was diagnosed as showing an unusual type of histiocytoma. Ganglioneuroma was ruled out by the absence of Nissl granules with thionin stain. When the sections were submitted to general and surgical pathologists, however, the diagnosis of myoblastoma was favored. I reviewed sections of biopsy specimens from Dr. Allington and Dr. Templeton's case, and slides from the two cases were presented with a tentative diagnosis of myoblastoma at the dermatopathological round table at the December, 1950, meeting of the American Academy of Dermatology and Syphilology in Chicago. Dr. Caro at that time pointed out the similarity of both cases clinically and histologically to his case. We all agreed that, while the cells looked like those of granular-cell myoblastoma, definite granules could not be demonstrated in the cells. In retrospect, the arrangement of the cells in Dr. O'Leary's and my case with multinucleated giant cells and many pale-staining histiocytes fits perfectly that in Dr. Senear and Dr. Caro's case of reticulohistiocytoma cutis. Our patient continued to exhibit progressive deterioration in general health, and nodules developed in the lungs. She showed temporary improvement after hospitalization and administration of cortisone, only to have a relapse recently.

I wish to acknowledge that I vacillated in my histologic diagnosis of various biopsy specimens from Dr. Allington and Dr. Templeton's case, which Dr. Allington will discuss. Zak, using the term reticulohistiocytoma, described four patients with solitary lesions but felt that the condition was the same as the cutaneous ganglioneuroma of Montgomery and O'Leary. In one case these authors did a toluidine blue stain but failed to mention the presence of any granules. There is no mention of Nissl granules in any of their cases or in the two cases of Dr. Arthur Allen. I am certain that Zak's Case 3 is the same one that was seen by Dr. Sims, of New York, to whom I wrote in 1944 that I thought the lesion was not a ganglioneuroma but an unusual form of histiocytoma. I do not believe these cases of Zak or Allen should be confused with cutaneous ganglioneuroma.

In reviewing O'Leary's and my case of multiple ganglioneuromas of the skin (ARCH. DERMAT. & SYPH. **29**:26-52 [Jan.] 1934), a diagnosis which was refuted at the time by several pathologists, may I say that the patient had no systemic disturbance, evidence of joint symptoms, or thyroid disturbance, such as occurred in the patients with reticulohistiocytoma as just described? In our patient with ganglioneuroma, the lesions cleared centrally and migrated peripherally. There was spontaneous involution of the lesions, and there has been no recurrence 15 years later, the patient having remained in good health. Restaining of the original sections still reveals typical Nissl granules in ganglion cells. I have not been able to demonstrate Nissl granules with thionin stains in any of 12 cases I have seen since 1934 in which the diagnosis of ganglioneuroma has been suspected. The history in our case of incomplete rotation of the colon with increase in ganglion cells in the appendix also makes it seem likely that there is still the rare condition of multiple ganglioneuroma of the skin. It was in the involuting lesions in our case that one could see many histiocytes and multinucleated giant cells which differed in the character of the nucleus and nucleoli from true ganglion cells. (Clinical and histopathologic lantern slides were shown illustrating the differences among reticulohistiocytoma cutis, multiple ganglioneuroma of the skin, and granular-cell myoblastoma.)

DR. H. V. ALLINGTON, Oakland, Calif.: By way of discussion on this paper I am permitted to review a case which is in most respects closely similar to the two cases reported by Dr. Caro and Dr. Senear. The patient is a 66-year-old white woman who was presented before the

San Francisco Dermatological Society on Feb. 12, 1949 (ARCH. DERMAT. & SYPH. **62**:452-453 [Sept.] 1950). Early in 1948 she first exhibited areas of pinkish erythema and infiltration about the interphalangeal joints of her fingers and about her knuckles. These slowly progressed to form small, smooth, pale, pinkish nodules. They were tender when struck but not otherwise uncomfortable. She was known to have arterial hypertension, and a small goiter had been present for about 10 years. She was suffering from a chronic rheumatoid arthritis. The results of routine laboratory work were not unusual.

On treatment with potassium arsenite (Fowler's) solution orally and superficial x-ray therapy the lesions regressed for a time. However, in midsummer of 1948 they became more numerous and larger and spread to involve areas on the sides and palmar surfaces of the fingers and hands. They varied up to 1 cm. or more in diameter. A few lesions also appeared on the lateral surfaces of the forearms and elbows, the lateral malleoli of the ankles, the anterior surfaces of the conchae of the ears, the sides of the nose, and the chin. At this time tense, rubbery swellings suggesting ganglia appeared on the dorsa of the hands and wrists.

During this time the patient's arthritis was becoming severer and more extensive, with increasing pain, limitation of motion, and bony deformity, especially in the small joints of the hands, wrists, and shoulders. She was also losing weight, becoming increasingly nervous, and evolving the picture of a toxic adenoma of the thyroid gland. In September, 1948, her basal metabolic rate was + 60%. Blood cholesterol was 180 mg. per 100 cc. A chest roentgenogram showed an enlarged heart, arteriosclerosis, and pulmonary edema.

After therapy with propylthiouracil thyroidectomy was performed early in December, 1948. By February, 1949, the patient's general condition was noticeably improved, and she was gaining weight. By March, 1949, the skin lesions had begun to involute. They gradually became drier, flatter, shrunken, wrinkled, and horny.

This process of gradual improvement has continued to the present with respect to the patient's general health, her arthritis, and her skin lesions. Only a few shrunken remains of the nodules are now evident on the fingers.

Biopsy specimens showed a histologic picture with which we were not familiar, and sections were submitted to a number of our colleagues for their opinions. The diagnoses most commonly suggested were histiocytoma, myoblastoma, ganglioneuroma, and giant-cell sarcoma.

The principal change demonstrated in the sections is the appearance of collections of large cells with cytoplasm which stains pale red with hematoxylin and eosin and shows a velvety or ground-glass texture. The larger cells are multinucleated, many containing eight to a dozen or more nuclei scattered irregularly throughout the cells. The nuclei are only moderately enlarged, are vesicular or palely staining, and usually show one prominent nucleolus.

The abnormal cells are present throughout the whole cutis from just beneath the epidermis into the subcutaneous tissue. In most of the lesions the epidermis is stretched and thinned by pressure from below.

The large cells are separated by irregular fibrils and bands of collagen which take a normal red color with the Van Gieson stain. With this stain the cytoplasm of the large cells is colored a pale brownish-yellow. With Mallory's aniline blue stain the collagen stains greenish-blue and the cytoplasm pale violet. Sudan IV stain shows no fat in the cytoplasm. Prominent reticulum fibers are shown about and between the cells by Bielschowsky's stain. No elastic tissue can be demonstrated in the nodules. Mallory's phosphotungstic acid stain fails to demonstrate neuroglia fibrils. Giemsa-stained sections are a uniform pale blue, and thionin staining shows no definite chromophil granules in the cytoplasm.

The amount of inflammatory reaction present varies in different sections but usually is not marked.

Dr. Paul Fasal, of San Francisco, who recently saw the sections from our case, has suggested that histologically they show a great similarity to giant-cell tumors of tendon sheath origin (Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948, p. 1345; Willis, R. A.: Pathology of Tumors, London, Butterworth & Co., Ltd., 1948, p. 693). There were ganglion-like swellings on the backs of the hands and wrists in our patient and in one of the patients of Dr. Caro and Dr. Senear. This characteristic and the histologic picture both indicate a close relation between these skin lesions and a certain type of benign synovioma.

This case, the two of Dr. Caro and Dr. Senear, and those discussed by Dr. Montgomery parallel one another very closely both clinically and histologically. The microscopic picture in these cases is similar to that in the cases described by Zak.

Dr. Caro and Dr. Senear have done a great deal to clarify the picture and establish the abnormal cells as altered reticuloendothelial cells.

The widespread symmetrical distribution of the eruption and its association at times with general disease suggest that these lesions represent a skin reaction to some toxic process or metabolic defect. The spontaneous clearing which sometimes occurs, and which in our patient followed improvement in the coincident general disease process, also suggests this.

Dr. H. J. Templeton, Oakland, Calif.: While observing Dr. Allington's patient with him and studying the biopsy specimens, I reviewed the literature concerning similar cases and considered the opinions of Dr. Montgomery, Dr. Weidman, Dr. Caro, Dr. Ketron, Dr. Winer, our own neuroanatomists, and our own local pathologists who studied some of our slides. Dr. Broder and the neuropathologist at the Mayo Foundation studied others. The diagnoses which were made for our slides were ganglioneuroma, neuroreticuloendotheliosis, histiocytoma, myoblastoma, leukemia, giant-cell sarcoma, and luteoma.

Dr. Wilson, of Palo Alto, Calif., did some touch smear examinations on our patient and felt that the cells were in keeping with those of giant-cell fibrosarcoma. When men of such wide experience give us so many diagnoses, it is easy to see why Dr. Senear, Dr. Caro, and Dr. Allington have difficulty in identifying the origin of the primitive tumor cell. But as time goes on, and as these cases accumulate, a great deal is added to supplement our knowledge of the condition, which, I think, is a definite clinical entity.

Dr. L. H. Winer, Beverly Hills, Calif.: Histiocytoma has been considered by some as a type of subepidermal fibrosis. There is a difference, however, in that histiocytomas show phagocytes which can disappear spontaneously, wheras subepidermal fibrosis remains constant. Yet nosologically, histiocytoma is a simple type of fibrosis. Pathologists classify fibroxanthoma, which is a step further along in the progress of a histiocytoma, as a fibroma with xanthomatous changes. Thus, the fibrotic process is the final change in these lesions.

The cells arise from the reticulum cell, which is capable of undergoing two changes: (1) the formation of a histiocyte, which phagocytizes and may remain as a histiocyte, or (2) the formation of a fibrous connective-tissue cell, either directly or by going through the intermediate stage as a histiocyte., To me, the giant cells shown today were characteristic of xanthofibroma. Dr. Caro's second slide shows epithelial hyperplasia, which is characteristic in about 70% of the epidermis directly above the histiocytomatous tissue. This may be so extreme at times as to be suggestive of pseudoepitheliomatous hyperplasia.

Dr. Allington's case, which was mentioned by the essayists, was considered at one time to be a luteoma, a tumor which occurs in women past menopause and spontaneously disappears. This can be associated with thyroid deficiency, as was the case in Dr. Allington's patient. We had occasion to study this patient's tissue and stained it for nerve fibers but were unable to demonstrate nerve fibers or Nissl bodies.

In Dr. Montgomery's case, which was described as ganglioneuroma in 1934, we removed a section when I was in Minneapolis and diagnosed the condition as xanthoma. Reticulated cells, giant cells, and eosinophiles are frequently found in xanthoma, and especially in xanthoma diabeticorum. The presence of fibrous connective tissue around the reticulated cells indicates that the reticulum in the center is phagocytizing, whereas the reticulum at the periphery is undergoing fibrosis.

In summary, the reticulum undergoes xanthomatous or histiocytic changes which can eventuate in fibrosis and complete disappearance. Nosologically, the reticulohistiocytoma is related to the xanthofibroma and to the histiocytoma.

Dr. Herman Beerman, Philadelphia: Through the courtesy of Dr. Weidman two years ago at the round table of the American Academy of Dermatology and Syphilology I presented a patient with a definite example clinically of Dr. Montgomery's ganglioneuroma. At that time Dr. Montgomery agreed that the lesion was a ganglioneuroma. The initial stains were not positive, but they led me to wonder whether the stain is always positive when it should be.

My second point is that the lesions of the patients whom Dr. Caro and Dr. Senear, Dr. Allington, and Dr. Montgomery have presented remind me so much of the benign giant-cell tumor of the tendon sheath that I should like to know how the two are differentiated. Certainly, in their patients there are joint lesions, or at least lesions around the joint, which, as I recall, are not present in the patients with ganglioneuroma.

Dr. Oscar Gans, Frankfurt, Germany: I should like to show you photographs of a patient with lesions that are somewhat similar to those of the patients just presented. The patient, aged 44, had lesions on the extensor surfaces of the skin for the past year. Biopsy was performed on one of the lesions of more than six months' duration. Later, the patient exhibited an acute eruption of only a few days' duration, and biopsy was made of one of these lesions. The latter sections simulate those shown by Dr. Montgomery from his case of ganglioneuroma. Many of the cells in these sections from my case appear to be lymphocytes, but in between one sees larger cells which are very much like the histiocytes shown in the previous cases. We did not see giant cells as shown in Dr. Caro's lantern slides.

In 1906 Joseph Jadassohn published a report of a case under the title of pseudoleukemic infiltration of the skin, and the patient was still alive in 1922. Similar cases have been reported under the diagnosis of lymphocytoma. Only if proliferative centers of lymphocytes are seen in the nodules can one distinguish between benign cells and those of malignant lymphosarcoma.

One may feel inclined to consider this condition as merely a hyperplastic reaction of a pre-existing lymphatic tissue. However, in sections that I have taken of older lesions, cells were observed that were very similar to those presented by Dr. Montgomery from his case resembling Dr. Caro's, namely, large cells with pale-staining cytoplasm and nucleus which might be mistaken for xanthoma cells if it were not that they contained no cholesterol. I should like to ask Dr. Caro about the time elapsed between the development of the papules and the biopsy. If one performs a biopsy within two or three days, one may obtain an entirely different picture from those we have seen here, which I consider a late local reaction in a tumor-like eruption.

Dr. Fred D. Weidman, Philadelphia: I agree that the lesion histologically is a histiocytosis. I also agree that, from the clinical standpoint, the designation reticulohistiocytoma cutis is a proper one. However, from the standpoint of processes, I doubt that it is a true neoplasm. Thus, we noticed in the color illustrations of the patients on the screen that there was a large inflammatory factor in certain of the lesions. Also, the distribution upon points of pressure speaks in favor of the presence of some irritant factor which must have played a part in the production of the reaction. Accordingly, I would agree to the suffix "oma" only in the sense that it is used in the case of nodular subepidermal fibrosis. It connotes simply that a swelling is produced.

From the standpoint of the histologic reaction, the lesion is not a genuine neoplasm. It falls more in the category of the granulomas, and, incidentally, I think that this is true also of nodular subepidermal fibrosis. On that basis, there is an irritative factor also in Dr. Gans's cases; the reticulohistiocytic reaction would be directed against the leucotic elements which had become degenerated. I had not thought of leukemids as a basis for these lesions; they present an explanation for the generalized, widespread distribution of the lesions in certain patients.

In the final analysis we are dealing with a reaction against some irritant. Ordinarily, that reaction is effected by means of the exudative cells of the blood stream (leucocytes), histiocytes, and fibrosis. But I take it that in the cases presented this morning the reaction is on the part of the reticuloendothelial system; I suspect that there is a peculiarity in the constitution of the individual patient whereby reticuloendothelial tissue becomes the reactive factor.

Reticulohistiocytoma cutis can be reconciled very nicely with subepidermal nodular fibrosis by substituting the reactive cell of the latter (fibrocyte, histiocyte) for the reticulohistiocyte of the reticuloendothelial system. The presence of lesions apart from points of pressure, as in the cases shown on the screen in which there were myriads of lesions, might be explained on the basis that the irritant is occurring in connection with other kinds of lesions, such as folliculitis, or even the leukemids which Dr. Gans discussed.

Dr. Marcus Caro, Chicago: Dr. Winer discussed this lesion as being a possible variant of xanthoma. In xanthoma and in fibroxanthoma the Sudan III stain shows the presence of much fat, which stains brilliantly red in all the foam cells and giant cells. The amount of fat present in our case was so slight that in some sections it was difficult to be certain that fat was present

at all. This should rule out any form of xanthoma as a possible diagnosis here. In addition, in none of the sections taken from various lesions in the two cases we are reporting did we find any pseudoepitheliomatous hyperplasia. This was one of the features that helped us to differentiate this lesion from that of myoblastoma.

Dr. Beerman asked about this lesion's possible relation to the giant-cell tumors of the tendon sheath. It is difficult at times to differentiate the two types of lesions. As I pointed out before, vital staining with colloidal iron is necessary to identify with certainty the cells of reticulohistiocytoma. I have not done this staining in any case of giant-cell tumor of the tendon sheath. The fact that many of the lesions in our cases were present on the scalp, nose, ears, forearms, and chest, however, tends to make any confusion with that disease hardly possible.

Dr. Gans showed slides of sections which, in my opinion, had no possible connection with the cases under discussion. His sections seemed to represent forms of reticuloendotheliosis, and in no slide did I see any of the multinucleated giant cells upon which we base the diagnosis of reticulohistiocytoma. He also asked about the age of the lesions that were examined histologically. In our first case lesions have been appearing at frequent intervals, even up to the present. We performed biopsies on eight or nine different lesions in various stages of development, those on the ears and scalp being a few weeks old, while some on the fingers were several years old. We found the lesions in all specimens at all ages to be composed of these unique multinucleated giant cells. The giant cells were few, and they lay just beneath the epidermis in young lesions, but as the lesion became older the area affected became larger and much more deeply located in the corium.

I agree with Dr. Weidman that this is not a neoplasm but some kind of inflammatory reaction. We have kept the name reticulohistiocytoma because the designation is already established in the literature.

From the number of cases that have been mentioned here in the discussion, it is apparent that reticulohistiocytoma is not a rare disease. We cannot, as yet, be certain whether it is a specific disease or merely represents some pathologic reaction in the skin that may be produced by many disease processes. In our first case the finding of iron in the giant cells on microincineration suggests that at least in some cases a foreign-body reaction may be the pathologic process involved.

Whether this is a new entity or merely one which is very old and is just now being recognized more frequently, we cannot be certain. From our own experience, however, we can say that in more than 13,000 specimens that we have examined in our laboratory during the past 22 years we have never before come across an identical histopathologic picture. In only one previous case, the one reported subsequently by Montgomery and O'Leary,[4] did we find histopathologic features that suggested this condition at all. Even in that case, however, staining with thionin blue demonstrated the presence of Nissl granules, and these granules cannot be found in the giant cells of reticulohistiocytoma.

# FALLACIOUS FAILURE RATES IN TREATMENT OF EARLY SYPHILIS

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SOME will accept, some reject the following ideas, but most persons will reflect upon them and give them further thought. That is enough.

During the last seven years much literature has accumulated on the treatment of early syphilis with penicillin. Generally speaking, the total dosage of penicillin has varied from a minimum of 300,000 units to a maximum of 10,000,000 units per patient. Published cumulative failure rates have varied from a minimum of 4 or 5% to a maximum of 50%. Practically all published data on failure rates have included cures listed as failures.

Much stress has been placed by noted authorities on an intrinsic over-all failure rate of about 20% in the treatment of early syphilis with penicillin. With this conclusion, I am in complete disagreement, I contend that the failure rate is entirely too high.

The purpose of this paper is to point out that the reported failure rates must, of necessity, be specious. They are based, at best, on a minority group designated as true failures, and a majority group that is made up of patients in whose blood serum a reagin-like substance, specific or nonspecific, has unfortunately been retained or developed, and of patients who have acquired reinfections, symptomatic or asymptomatic.

With the oft repeated statement to the effect that there is no manner in which to differentiate between relapse and reinfection I must disagree. In most instances the objective data, particularly that of epidemiologic nature, necessary for the differential diagnosis, is unavailable. Without complete objective data the differentiation is usually impossible; however, with the required objective data it is usually possible to differentiate between relapse and reinfection. This my associate and I were able to do in a previous study.[1] Lack of such data in the majority of cases makes any statistical study on this subject inaccurate, since all reinfections are arbitrarily placed in the failure group.

Even more difficult is the differentiation of serorelapse from reinfection. Reinfection can occur without the associated clinical lesions of primary and/or secondary

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Read at the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 25, 1951.

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1. Schoch, A. G., and Alexander, L. J.: Reinfection and Relapse After Treatment of Early Syphilis with Penicillin, Arch. Dermat. & Syph. **60**:683-700 (Nov.) 1949.

syphilis. Magnuson [2] has shown in animal experiments that asymptomatic reinfection in the rabbit is the rule rather than the exception when reinoculation takes place later than the treated primary stage in the course of the disease. Many clinicians, including myself, have thought for years that reinoculation and reinfection can and do occur in man frequently without the development of a second primary lesion or a second episode of secondary syphilis, evidenced only by an upward swing of reagin in the blood serum and possibly only by a persistent reagin titer which is ordinarily spoken of as seroresistance or "Wassermann fast."

We [3] previously reported reinfection in husband and wife in the pre-penicillin era, with a span of over five years between the two infections in this couple. During this span both were clinically and serologically normal. The wife had a second primary lesion (tonsillar) with large sparse typical secondary syphilids on the skin. The husband had only a "red throat" and a high serologic titer as evidence of his reinfection. For the original infection the husband was treated during the secondary stage, presumably obtaining more effective immunity than his wife, who had primary syphilis at the time.

Patients who have had similar experiences during the course of their follow-up after a single course of penicillin treatment for early syphilis have been categorically placed in the failure group, admittedly for statistical reasons, but certainly in error.

In addition to syphilis, Rein [4] has elaborated upon 40 or more nonsyphilitic infections and conditions which are capable of producing biologic false positive reagin-like substance in the blood serum. The fact that biologic false positive reagin-like substance exists has been accepted by all. In any patient who has been successfully treated for early syphilis with penicillin such biologic false positive reagin may develop in the blood serum during the ensuing months or years of observation. If this occurs, it is customary, in all large-scale statistical evaluation studies, to relegate these patients to the failure group, either in the category of serorelapse or that of seroresistance.

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2. Magnuson, H. J., and Rosenau, B. J.: The Rate of Development and Degree of Acquired Immunity in Experimental Syphilis, Am. J. Syph. **32**:418-436 (Sept.) 1948.

3. Schoch, A. G., and Alexander, L. J.: Reinfection in Syphilis, Am. J. Syph. **27**:15-29 (Jan.) 1943.

4. Rein, C. R.: Problèmes relatifs au sero-diagnostic de la syphilis, in Colloque International sur la Syphilis, Organization Mondiale de la Sante, Paris, Sept. 25-Oct. 7, 1950, Prophylax. antivén. **22**:500-512 (Nov.) 1950; Serodiagnosis of Syphilis: Recent Advances, J. Michigan M. Soc. **46**:541-549 (May) 1947; The Serologic Tests in Penicillin-Treated Syphilis, New York J. Med. **47**:2450-2452 (Nov. 15) 1947. Rein, C. R., and Kostant, G. H.: Lupus Erythematosus: Serologic and Chemical Aspects, Arch. Dermat. & Syph. **61**:898-903 (June) 1950. Chargin, L., and Rein, C. R.: The Reliability of Serologic Tests for Syphilis, J. Mt. Sinai Hosp. **12**:111-115 (May-June) 1945. Barnard, R. D.; Rein, C. R., and Doan, C. A.: False Positive Serologic Tests for Syphilis Following Blood Donation, Am. J. Syph. **30**:255-263 (May) 1946. Scott, V.; Rein, C. R.; Schamberg, I. L.; Moore, J. E., and Eagle, H.: The Serologic Differentiation of Syphillis and False Positive Sera, ibid. **29**:505-528 (Sept.) 1945. Rein, C. R., and Elsberg, E. S.: False Positive Serologic Reactions for Syphilis with Special Reference to Those Due to Smallpox Vaccinations (Vaccinia), ibid. **29**:303-312 (May) 1945; Studies on the Incidence and Nature of False Positive Serologic Reactions for Syphilis, Am. J. Clin. Path. **14**:461-469 (Sept.) 1944.

Alexander and I [5] reported in detail the case of one particular patient with residual syphilitic reagin in the blood serum who exhibited sharp rises in reagin titer, obviously due to exacerbations of lung abscesses. Intercurrent, nonsyphilitic infections, varying in severity from the common cold to pneumonia, are probably capable of restimulating the reagin production mechanism, with resulting sharp rises in reagin titer. In addition, I believe pregnancy, capable of producing reagin-like substance in a nonsyphilitic woman, is also capable of producing or increasing this substance in a woman who has been previously treated for syphilis. When this happens, a fallacious diagnosis of serorelapse becomes a certainty.

## LABORATORY FINDINGS

No syphilis clinic is any better than the laboratory that performs blood and spinal fluid examinations. Regardless of how carefully controlled are the serologic tests, regardless of state or national ratings in serologic surveys, regardless of author-serologists' supervision, there are certain intrinsic factors of error in serologic tests for syphilis as currently performed. In addition, there exist clerical errors which have to do with labeling of test tubes, writing of reports, transferring reports to patients' records, and duplication of patients' names. Add to these possible local clerical errors the possible clerical errors at the Central Tabulating Unit, and the element of human error begins to be statistically significant.

For obvious reasons at our clinic we have sent all blood and spinal fluid specimens to two different laboratories, simultaneously, for approximately 15 years. A discrepancy in the reports of these two laboratories, both using multiple serologic tests for syphilis, usually has meant clerical or technical error—a new assistant serologist, a change in the lot of antigen, the absence of the head serologist on vacation, or illness in the record clerk's family, to mention only a few of the human factors which govern the accuracy of reported serologic tests for syphilis.

I wish to stress the fact that no one laboratory, regardless of how well controlled or how efficiently operated, is accurate enough to exclude all instances of technical or clerical error in performing and reporting serologic tests for syphilis. Two laboratories reporting simultaneously on all specimens are mandatory to reduce this factor of error, because otherwise a false positive reading or a false negative reading on a given serum is recorded and accepted at face value. Even if the reading is repeated in order to substantiate the findings, the same report is often received, particularly from conscientious serologists who pride themselves on consistency.

These fallacious reports are interpreted and recorded as "serorelapse," "declining titer," or "Patient has become seronegative." Subsequent tests reflect "satisfactory response to retreatment," "serorelapse," or "occult reinfection." All could be erroneous without the knowledge of the serologist, the clinician, and the statistician! Nevertheless, and of necessity, all these errors are and have been included in statistical studies of the penicillin treatment of syphilis.

A simple expedient we have used for years to enable us to recheck serologic tests for syphilis is to send all specimens to the serology laboratory numbered serially, beginning with the first of each month. Rechecks can then be sent as often as

5. Schoch, A. G., and Alexander, L. J.: Unusual Behavior of Syphilitic Reagin Following Intensive Treatment of Early Syphilis, Am. J. Syph. **28**:305-309 (May) 1944.

desirable; the numbers on repeated specimens of blood and spinal fluid are always different. Bizarre serologic patterns are often recognized by our head serologist without helpful clues, such as names or clinic chart numbers.

Frozen specimens of blood serum are of additional value occasionally and, if properly selected, shed considerable light on the consistency with which the serologic tests are performed.

To classify as treatment failures patients who exhibit minor spinal fluid changes, such as pleocytosis and a slight increase in quantitated spinal fluid protein, with or without partial colloidal curve changes, but with negative spinal fluid complement fixation reactions, is erroneous. These spinal fluid changes lack proof of specificity and should be regarded as nonsyphilitic in origin until proved otherwise. Should these spinal fluid findings, however, make their appearance or be detected during the primary or secondary stage of the disease, I would agree to their probable syphilitic origin. If they are observed, however, in subsequent months or years of follow-up, in patients who have had early syphilis, well treated with penicillin, this does not mean neurorelapse unless so proved. These patients should not be relegated to the category of failure. It is erroneous to consider these nonspecific spinal fluid findings as syphilitic in origin without proof.

Fifteen years ago I studied 60 patients who had been under treatment for syphilis with arsenic and bismuth. They exhibited spinal fluid abnormalities of this minor nature 6 to 12 months after the initiation of treatment. The original diagnosis was early syphilis or early latent syphilis. If they had been receiving weekly injections of bismuth, these were continued; if they had been receiving weekly injections of an arsenical, these were also continued. However, spinal fluids of these patients were reexamined from one to three months later, and in every instance the minor changes had disappeared and the spinal fluid had returned to normal. In all instances in which the original spinal fluid examination showed minor abnormal changes, upper respiratory infections of varying degrees—usually the common cold of a rather severe type—were present at the same time. All these patients were ambulatory. The incidence of these abnormal spinal fluids was found to be unusually high during the winter months, and it was this observation that led us to concentrate on upper respiratory infection as a probable explanation for transient but definite spinal fluid abnormalities. We came to the conclusion that a severe common cold was capable of producing a pleocytosis, increase in spinal fluid protein, and a low midzone colloidal gold curve, but always unassociated with any change in the spinal fluid Wassermann reaction.

When the above group of patients, though minor in number, is included in the category of treatment failures in statistical surveys, it adds to the number of those falsely classified as failures.

In any nation-wide survey, regardless of the quality or caliber of the venereal disease clinics entering into the investigation, such factors of error as those mentioned are unavoidable. However, the central statistical units evaluating these data, which are sent by mail, must accept positive or negative findings as transmitted to them. They have no alternative but to accept the unavoidable errors in the serologic tests from not only one clinic but many clinics, thus increasing the error that emerges from the tabulating machine over and above that which perhaps would come from one individual clinic. In this connection, the sharp reduction in case numbers of all types of syphilis probably precludes a large-scale evaluation study of treatment

of any phase of the disease with the other antibiotics and the newer drugs to come. Our present evaluation studies of the past decade, even if repeated in the next 10 years, still would be subject to the same fallacies.

Even if Nelson and Mayer's [6] recent work on immobilizing antibodies were today simplified to the point that it could be or would be in general use throughout the major venereal disease clinics throughout the country, there still would exist certain intrinsic and extrinsic factors of error in large-scale evaluation studies of the treatment of early syphilis when pooled data are subjected to central statistical analysis.

Paul O'Leary,[7] at the 1950 meeting of the American Academy of Dermatology and Syphilology, reported a long-term, five-year follow-up study on early syphilis from patients treated at the Chicago Intensive Treatment Center. This study was made possible by Bundesen's enthusiastic cooperation in bringing these patients back for reexamination, during which time, to quote O'Leary, "Everything else in public health in Chicago stopped." Of about 600 patients culled for reexamination five years after treatment for early syphilis, slightly over 100 had been re-treated; others had been lost from observation or re-treated at other agencies. Slightly over 200 patients were available for reappraisal. All but six were clinically and serologically normal, and these six had only traces of reagin left in the blood serum. A third of the 600 should have attained economic, emotional, marital, and social stability in a five-year period. Yet only a third remained for five-year appraisal, a proportion numerically and statistically insufficient. Having intimate knowledge of the penicillin problem since 1943, I believe Chicago could best evaluate five-year results on the basis of data emanating from a single clinic or treatment center.

The necessity for long-term observation of patients who have received penicillin treatment for early syphilis was again stressed recently by O'Leary, as it had been previously by many other outstanding syphilologists. It is my present contention that any long-term study in the evaluation of early syphilis—5, 10, 15, or 20 years—will be subject to more factors of error than short-term studies already reported in the literature with a follow-up period of from 12 to 20 months. The intrinsic percentage of "lost from observation" in a 20-year period is, of necessity, a majority group. This O'Leary found to be true in a five-year follow-up. This Brucegaard also found to be true, as did Padgett [8] when he investigated the results of the treatment of latent syphilis, and as did Stokes,[9] Moore,[10] Dudley Smith,[11] and others when they attempted long-term follow-up studies approximating 20 years in amplitude.

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6. Nelson, R. A., Jr., and Mayer, H. E.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. **89**:369-393 (April) 1949; cited by Nelson, R. A., Jr.; Zheutlin, H. E. C.; Diesendruck, J. A., and Austin, P. G. M., Jr.: Studies on Treponemal Immobilizing Antibodies in Syphilis, Am. J. Syph. **34**:101-121 (March) 1950.

7. O'Leary, P. A.: Five-Year Follow-Up Study of Early Syphilis, From Patients Treated at the Chicago Intensive Treatment Center, read at the Ninth Annual Meeting of the American Academy of Dermatology & Syphilology, Chicago, Dec. 2-7, 1950.

8. Padgett, P.: Personal communciation to the author.

9. Stokes, J. H.; Beerman, H., and Ingraham, N. P.: Modern Clinical Syphilology, Ed. 3, Philadelphia, W. B. Saunders Company, 1944.

10. Moore, J. E.: Modern Treatment of Syphilis, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943.

11. Smith, D. C.: Personal communication to the author.

Long-term studies invariably consist of reexamination years after treatment, in the main ignoring interim episodes of all illness and treatment. First of all, there exists a select group of survivors. Secondly, long-term observation periods fail to record what has happened to a given patient in the interim period. During this interim period of 1 to 20 years, syphilis, treated or untreated, could be reacquired several times after the original infection. In addition, intercurrent infections yielding biologically false positive reactions would be expected to make their appearance. Pregnancies, logically expected, would be in evidence. Spontaneous cures following inadequate treatment of the original infection, as well as spontaneous cures of subsequent infections (reinfections) would be expected in certain instances. Furthermore, in the antibiotic era, penicillin or other antibiotics, such as aureomycin (Kierland and O'Leary [12]) and terramycin (Schoch and Alexander [13]), in all probability would have been given to patients repeatedly for suspected or actual nonsyphilitic infection, and would have exerted a partial or total curative effect on syphilis, diagnosed or undiagnosed. Therefore, many patients with syphilis undiagnosed but cured and many with reinfection undiagnosed and not cured confuse the observer on long-term studies.

For the last 10 years syphilis has been regarded by many of us dealing with the disease firsthand as an acute infection rather than a chronic one. If one is to evaluate results of treatment in an acute disease, one cannot approach the problem on the basis that it is a chronic disease, similar to tuberculosis, lasting over a period of 20 or 30 years, and arrive at a conclusion which approximates truth.

Many of us who have dealt with early syphilis since the beginning of the intensive therapy era have been impressed with the rapidity of response to treatment. We, furthermore, have been impressed with the tremendous number of reinfections, a subject in which I have been profoundly interested for almost 20 years.

My sincere belief has been that since the advent of rapid treatment, particularly penicillin, reinfection occurs more frequently than relapse. Fortunately our recorded data have been substantiated by Peabody and Webster.

Long-term observation of contacts treated by any abortive measure is fraught with even more inaccuracies when subjected to statistical analysis than is the evaluation of early syphilis. A normal person exposed to infectious syphilis who has received abortive treatment during the incubation stage of the disease and who remains clinically and serologically normal for a period of six months, or at most a year, should be considered protected against the acquisition of early syphilis. This should be accepted, unless one assumes that a treated contact practices complete abstinence from all intimate contacts, including sexual intercourse, during the observation period, an assumption, which, of course, is absurd. If inoculation immunity to reinfection is a fluid state, as Magnuson's studies indicate, and varies from nil to effective during the primary and secondary stages of the original infection, then hypothetically all contacts treated for known exposures are devoid of all immunity; whereas, in some patients with primary and particularly in some with secondary syphilis effective immunity is developed prior to treatment of the first infection.

12. Kierland, R. R.; Herrell, W. E., and O'Leary, P. A.: Treatment of Syphilis with Aureomycin Administered by Mouth, Arch. Dermat. & Syph. **61**:185-195 (Feb.) 1950.

13. Schoch, A. G., and Alexander, L. J.: Terramycin in the Control of Venereal Diseases, Ann. New York Acad. Sc. **53**:459-460 (Sept. 15) 1950.

SUMMARY

During the past seven years we have learned that penicillin treatment of early syphilis cures the majority of patients who receive it. We have also learned that they are vulnerable and susceptible to reinfection and susceptible likewise to intercurrent infections which might provoke or produce biologic false positive reagin-like substance; that 5- to 20-year follow-up of patients treated for early syphilis interjects into the long-term follow-up period factors of error which are complete and numerous; and that the fallacies of present-day serologic tests for syphilis are reflected in our present-day method of technical, clerical, clinical, and statistical evaluation studies of the treatment of syphilis.

CONCLUSIONS

I think an honest and perhaps an inevitable mistake has been made in evaluating the curative power of penicillin in early syphilis. Published cure rates are too low, according to our own and other data.

I believe long-term observation of treated patients is a poor approach to the real answer as to what percentage of patients with early syphilis are cured by a single adequate course of penicillin treatment.

I believe, furthermore, that obsolete dictums such as "No treatment of syphilis without a proved diagnosis," etc., should take their place with Jonathan Hunter's teaching (syphilis and gonorrhea—the same disease) as of historical interest only and unacceptable today.

And I know that certain factors, particularly the grouping of reinfection with relapse, introduce fallacious elements into current evaluation studies that some of this generation will regret in the future.

## ABSTRACT OF DISCUSSION

Dr. L. W. Shaffer, Detroit: This interesting and typically dramatic paper by Dr. Schoch reflects his enthusiasm for the effectiveness of penicillin therapy of early syphilis, and his leadership in securing recognition of the fact that reinfection is the leading cause for re-treatment rather than clinical or serologic relapse. He coined the term "ping-pong" syphilis, which has swept the nation. He has effectively defended his title of "Fallacious Failure Rates" in this paper.

It is impossible in many cases to differentiate with accuracy between reinfection and clinical relapse. The possibility of asymptomatic reinfection, as demonstrated by Magnuson and evidenced only by a return to seropositivity or a marked increase in serologic titer, complicates the problem still further, and it becomes almost impossible to distinguish between serologic relapse as an evidence of treatment failure and reinfection. A valuable and commonly neglected means of differentiating between reinfection and relapse is epidemiologic confrontation. An investigation as to whether sexual contact occurred in a case of infectious syphilis within the limits of the appropriate incubation periods, although not necessarily conclusive, would be very helpful in many questionable cases.

The problem of how frequently reinfection occurs in contrast to relapse will depend upon the opportunities for reinfection. Patients who acquire venereal disease are generally very promiscuous and travel in a social stratum where syphilis is more prevalent. Their chances for reinfection are much greater than for the population at large. Secondly, the chance for reinfection will be much greater if a high incidence of infectious syphilis is present in the community. The frequency of reinfections should be much less today than in 1946, when the incidence of infectious syphilis was very much higher. This may explain in part the improvement in therapeutic results reported from more recent schedules of penicillin therapy.

A third and a most important cause of frequent reinfections is the failure to find and control the infectious contacts in such cases. This is difficult at best with short-course intensive penicil-

lin treatment since in many cases it does not permit sufficient time to find the infectious contacts. If adequate control of such infectious sexual contacts is not secured, Dr. Schoch's "ping-pong" syphilis can be expected to occur in almost every case. The old style, prolonged heavy metal therapy, although permitting more reinfections than commonly recognized, often protected the patient against his contacts until their infectious lesions spontaneously healed.

Margaret Merrill, statistician at Johns Hopkins University for the nation-wide study of penicillin treatment of syphilis, reported at the Symposium on Recent Advances in the Study of Venereal Disease, held in Washington, D. C., April 24-25, 1951, that the monthly reinfection rates for Negroes treated in the Dallas and Galveston groups were more than twice as high as for similar colored patients treated in the Bellevue and Chicago groups. She also estimated that reinfections represented 55% of the failures among the Bellevue Negroes receiving the most successful treatment and 25% for the least successful treatment, at 18 months. This is the first statistical information that I have heard confirming Dr. Schoch's claim that the majority of failures in cases of well-treated early syphilis are due to reinfection. It would also establish the fact that reinfections could be expected to occur more frequently in his cases than in a similar group in the North.

It is necessary to classify re-treatment cases as treatment failures in the absence of any satisfactory means of differentating between reinfection and relapse. It is consoling, however, to know that reported re-treatment rates are not true failure rates and that the incidence of biologic cure is much higher than re-treatment rates would indicate. The longer the follow-up the greater the percentage of re-treatment cases that will be cases of reinfection. Among patients originally treated for primary and secondary syphilis with an approved penicillin schedule and followed for 18 to 24 months, it can be expected that approximately 50%, even a higher percentage in Texas, of those re-treated will actually have been reinfected.

C. R. Rein, New York: Dr. Schoch is to be highly commended on his excellent and timely philosophical remarks dealing with "Fallacious Failure Rates." For the past seven years he has strongly disagreed with those who have reported high cumulative failure rates following penicillin therapy in early syphilis. He has believed that many of the so-called failures were probably symptomatic and asymptomatic reinfections. That asymptomatic reinfections can and do occur has been demonstrated by Arnold's group and by Magnuson in their animal experimentation.

It has been quite apparent to many of us that the incidence of symptomatic and asymptomatic reinfections will depend on the infectious reservoir in the patient's environment. This is well borne out by the results of a recent experiment by D. E. I. Grin of Yugoslavia in an isolated village in Bosnia where there was little or no migration. Examination was made of the entire population of 330, of which 66% had positive serologic reactions for syphilis and 48.5% had early endemic syphilis. The entire syphilitic population was treated with 3.6 million units of penicillin. When these patients were reexamined 16 months later (in August 1950), 72% had attained and maintained seronegativity and the remaining 28% had shown a definite decrease in serologic titer, indicating a favorable response to therapy. There were no patients with seroresistance, serorelapse, or clinical relapse; and, what is of more importance, there were no reinfections.

Penicillin can be compared with a cake of soap; when used properly it will clean up a dirty person, but he will not remain clean if he plays around in a dirty back yard. Penicillin, when used in adequate dosage, will cure a patient with early syphilis, but it will not keep him cured if he continues to play around in a syphilitic environment.

Dr. Thomas H. Sternberg, Los Angeles: I want to congratulate Dr. Schoch for bringing this subject out into the open for discussion. Early in the course of penicillin studies of syphilis I was a member of the Penicillin Panel in which these nation-wide studies originated and in which it was decided to have this central tabulating unit. At that time the criteria which were set up for "cures" were so rigid and were so obviously weighted against penicillin that many of us, including Dr. Schoch and Dr. Rein and Dr. Mahoney, felt that the results that came out of this central tabulating unit would not reflect the true value of penicillin in the treatment of syphilis.

About a year and a half later Dr. William Leifer and I collected data on 1400 patients with early syphilis who had been treated in the Army with 2.4 million units of penicillin over a period of seven and a half days (Sternberg, T. H., and Leifer, W.: Treatment of Early Syphilis with Penicillin, J. A. M. A. **133**:1-5 [Jan. 4] 1947). Our over-all results on this group of patients, in which some 85% had a 9- to 18-month follow-up were 90% satisfactory, despite the fact that we were conservative and considered all possible reinfections as relapses and low titer serologic reactions at the end of the year as failures. These data were not submitted to the central stastistical unit or included in accumulative failure rates but were merely reported. The results were so good that many doubted their validity. It has been rather gratifying to Dr. Leifer and to me as time went on to find that if any error exists in these data it is on the conservative side.

In that paper we also considered the question of the disproportionate "relapse" rate among white patients versus Negroes. We had 790 white patients in whom there were 40 failures, or 5%, as contrasted with 92 failures in 610 Negroes, or a failure rate of 15%. We pointed out in the paper that, unless one considers that there is a marked difference in the host-parasite relationship between the two races, the only other explanation for this dissimilarity must be reinfection. This theory is supported by the fact that in the Army the syphilis rate was consistently much higher in the Negro race, and therefore one would expect that the reinfection rate would also be higher, as was brought out by our data.

DR. SCHOCH: It is particularly pleasant to have one's good personal friends discuss one's paper. As you can see, all the remarks have been flattering but possibly flavored by personal friendship. I appreciate them just the same. I was interested in Dr. Rein's remarks about the small village. He acquainted me with this study at the Academy meeting, but now his observation periods are much longer, of course. I was a little amused when he said this was a small community in which there was practically no migration. If one considers that 48% of the entire group in this village had early infectious syphilis, there must have been a little migration of at least one syphilitic into the community before this study was made. I think the figures are very impressive as he related them.

In conclusion, some of you naturally are going to say, "Well, if you disagree with the 20 to 30% over-all failure rate in the treatment of early syphilis, what is the true failure rate?" I personally think it is less than 5% in early syphilis (primary and secondary syphilis). I also have letters from at least a dozen colleagues, all men who have spent much time and energy in the study of treatment of early syphilis in the past six or seven years, and you should be interested in knowing that invariably they, too, believe the true failure rate is less than 5%.

# Clinical Notes, New Instruments and Techniques

## NEWER AND PROPOSED ELECTROLYSIS NEEDLES

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PLAINFIELD, N. J.

A variety of needles are available for the removal of superfluous hair. The long, stiff needles in common use among dermatologists are not the best for this purpose. Lay electrologists in general prefer a platinum-iridium needle which is adapted for gentle insertion into the hair follicle. This needle has an extremely narrow diameter of about 0.005 in. (0.013 cm.). It is flexible but can be pushed easily through a tight hair follicle. Yet it is soft enough to buckle when pushed into the skin near, but not into, the follicular opening. It is shorter than most other types of needles, measuring about 0.25 in. (0.64 cm.), but this is amply long for any hair follicle. Better control and accuracy and ease of penetration are obtained with these needle qualities. This type of needle is of equal value for use in the short-wave spark-gap and the galvanic-current machines.

Scarring of the skin occurs with the employment of any kind of needle and current now in use. The idea of an insulation coating on electrolysis needles to prevent skin damage has been advanced many times. No such insulated needle has proved of real value thus far. Considerable further research effort has been made to develop such a needle, and numerous materials have been tried. Such a needle coating must be extremely thin and have good dielectric qualities. Vitreous enamels and glass coatings were reported to me by competent authorities to be impractical for this purpose. Silicone resins were tried and found to be too thick. Various plastic lacquers seemed to offer a suitable material, but these did not stand up in use. Special wire enamels were employed but did not wear well. Accordingly, I wish to report these negative findings in this field, and I hope that a practical solution may yet be found.

## INFLAMMATORY RINGWORM DUE TO TRICHOPHYTON FAVIFORME

### Report of Two Cases

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NEW YORK
AND
DOROTHY FISHER, M.D.
STATEN ISLAND, N. Y.
With the Technical Assistance of F. E. Karpiuk, B.A.

Trichophyton faviforme, known since 1893, has rarely been isolated in the United States. In 1947, Fowle and Georg [1] reported 23 cases of suppurative ringworm contracted from cattle. These cases occurred in a farming community in central Pennsylvania. Cultural studies showed that 14 of these cases were caused by T. faviforme, and 4, by Trichophyton mentagrophytes. In the remaining five cases microscopic examination and cultures gave negative results, but the diagnosis of T. faviforme infection was made from the nature of the lesions and the history of contact

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1. Fowle, L. P., and Georg, L. K.: Suppurative Ringworm Contracted from Cattle, Arch. Dermat. & Syph. **56**:780-793 (Dec) 1947.

with ringworm-infected cattle. In 1949 Carney[2] reported 17 cases of T. faviforme infection occurring in Iowa farming areas. In most of the cases reported by Fowle and Georg, local treatment of the lesions proved of little value. They gave iodides intravenously and by mouth. Carney, however, stated that administration of mild fungicides and manual epilation were adequate.

The following cases occurred in two members of a family residing in Staten Island, N. Y., and are, to our knowledge, the first cases of T. faviforme infection reported from this area.

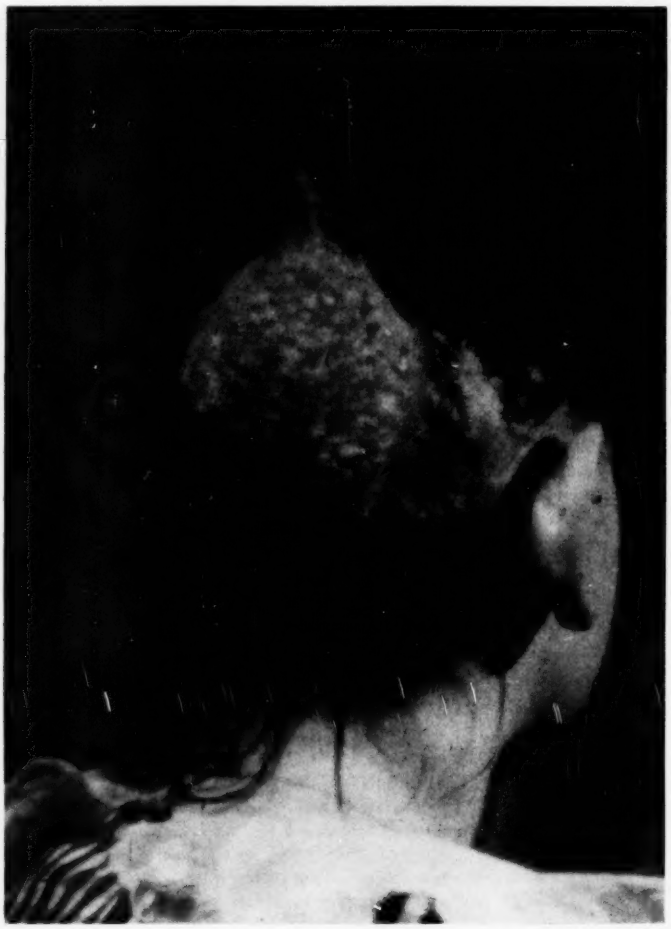

Fig. 1 (Case 2).—Kerion of the scalp due to T. faviforme.

REPORT OF CASES

CASE 1.—A. V., a white woman aged 30, was first seen in February, 1950, at which time she presented a slowly spreading eruption on the back, the chest, and the arms, of two weeks' duration. Two weeks prior to the onset of the rash the patient was in contact with a calf which

2. Carney, R. G.: Inflammatory Ringworm Due to Trichophyton Faviforme, Arch. Dermat. & Syph. **59**:209-216 (Feb.) 1949.

showed acute inflammatory lesions on its skin, with crusting and falling out of hairs. We had no opportunity to examine the animal, but from the description given by the patient it could be assumed that the calf was affected with ringworm. The eruption on the patient consisted of well-defined round plaques with erythematous vesicular borders and large polycyclic lesions with central clearing. Direct microscopic examination of skin scrapings and cultures revealed no fungi. The eruption was almost entirely gone in two weeks.

Fig. 2.—T. faviforme in a scalp hair. Potassium hydroxide preparation; × 500.

CASE 2.—F. V., aged 7 years, a daughter of the first patient, was first seen on April 11, 1950, two weeks after an eruption appeared on the face, the back, and the scalp. There was an annular erythematous plaque with pustular border and central scaling located in the right preauricular area. In addition, there was a blepharitis involving the margins of the right eyelids. Over the upper back there were several confluent gyrate lesions with pustular borders and a tendency to central clearing. Several areas of kerion formed rapidly on the scalp (Fig. 1).

These were large boggy masses studded with pustules and containing only a few hairs which did not fluoresce under the Wood light. Apparently the child had contracted the infection from her mother (Case 1).

Microscopic examination of skin scrapings showed no fungi. However, the examination of infected hairs from the scalp revealed numerous septate filaments, chains of spores, and scattered groups of spores on and around the hair. The large size of the spores (about 4 or 5 $\mu$ in diameter) and their disposition outside the hair suggested Trichophyton ectothrix megasporon (Fig. 2). Cultures from scalp hairs on Sabouraud's medium produced a colony which was identified as T. faviforme. The culture grew slowly and required a few weeks for full development. In the center there was a small elevation surrounded by irregular convolutions. The rest of the colony was flat and divided by radial grooves into several sectors. The border zone consisted of radiating feathery protuberances submerged within the medium and visualized on transillumination. The entire culture was glabrous and grayish, except for the central knob which was white

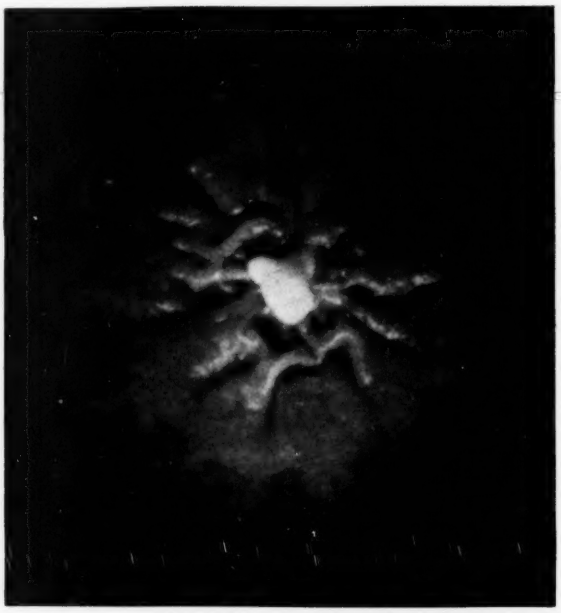

Fig. 3.—Culture of T. faviforme on Sabouraud's medium.

and velvety because of aerial mycelium (Fig. 3). Microscopic examination of a culture mount revealed septate and branched hyphae with numerous chlamydospores. Neither microconidia nor fuseaux were found. These features are known to be typical for T. faviforme growing on the standard Sabouraud medium. An unusual feature was the presence of a number of peculiar filaments, much thicker than the ordinary hyphae, with abundant protoplasm and knob-like swollen ends of bizarre shape. Hyphae with multiple terminal branchings were also seen, some of which resembled reindeer horns and closely simulated the "favic chandeliers" seen in cultures of Achorion (Trichophyton) schoenleini.

Treatment consisted of manual epilation, wet dressings with diluted Burow's solution (aluminum acetate solution), and the application of an undecylenic acid ointment. About one month after the onset of the fungous infection, a generalized eruption developed, consisting of small follicular papules. This was presumed to be a trichophytid, and it subsided in a few days. Continued improvement occurred until mid-June (three months after onset), at which time most of the eruption had disappeared from skin and scalp, and new hairs were growing in all the areas of alopecia.

SUMMARY

Two cases of inflammatory ringworm infection are reported. In one of the patients, a girl aged 7 years, Trichophyton faviforme was cultured. The other patient, the girl's mother, presented a clinical picture of an acute tinea circinata. Although the laboratory examination of the mother failed to reveal the presence of fungi, it may be assumed that the same fungus was the cause of her disease presumably contracted from an infected calf.

The infection in the adult responded rapidly to treatment. The naturally developing immunity and the topical measures were considered responsible for the therapeutic results. The infection in the child yielded after a longer period of conventional fungicidal therapy and manual epilation.

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201 Forest Ave., Staten Island, N. Y. (Dr. Fisher).

## CONTACT DERMATITIS DUE TO COLORED TOILET TISSUE

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Vulvar pruritus is a frequent complaint. The cause is difficult to discern, and the condition is complicated by reactions to medicaments used. With persistent and intelligent questioning, the so-called essential pruritus may be attributed to an original sensitizing agent, be it douching solution, nail polish, or, as in this case, colored toilet tissue.

### REPORT OF A CASE

A 25-year-old white woman complained of vulvar itching of four weeks' duration. The condition had become progressively worse, being aggravated by apparently the most innocuous topical remedies. Itching and burning were intense. On examination severe edema, oozing, and marked redness of the vulvar and pubic areas were observed. Initial questioning failed to reveal any suggestive causal factor. Routine medication was followed by some relief, but the condition failed to clear, although there were periods of improvement and recurrence. After two months, it was suggested that the use of toilet tissue be stopped and absorbent cotton substituted. The patient volunteered the information that for several months she had used toilet tissue in various colors. Improvement followed, and the condition cleared completely.

Samples of the toilet tissue of various colors, peach, rose, blue, green, and white were used for patch tests. A 4 + reaction to the blue tissue was elicited. A patch test for paraphenylenediamine gave a negative reaction. The dye in the toilet tissue was unknown. The patient has remained well for more than one year.

## SERUM SICKNESS FROM PENICILLIN

### A Report of Twenty-Two Cases

KATHLEEN A. RILEY, M.D.
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Since the first report on penicillin-sensitivity reactions by Keefer [1] in 1943, there have been many subsequent reports. Brown,[2] in 1948, reviewed the literature of 308 reports from 1943 to

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1. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, S., Jr., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections (500 Cases), J. A. M. A. **122**:1217-1224 (Aug. 18) 1943.

2. Brown, E. A.: Reactions to Penicillin, Ann. Allergy **6**:723-746, 1948.

1948. Beerman,[3] in 1949, summarized the status of penicillin-sensitivity reactions and stated that one of the most frequently reported clinical pictures is that of a serum-sickness-like reaction.

The first systematic study of the clinical and immunological phenomenon of serum sickness was done by von Pirquet and Schick [4] and was reported in 1905. Cecil [5] defines serum sickness as "allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period, skin eruption, enlargement of lymph nodes, fever, edema and polyarthritis." A similar syndrome has been reported as a result of the sulfonamides.[6] With the use of antibiotics, syndromes resembling serum sickness have been seen frequently resulting from penicillin. This syndrome has been reported most frequently as following intramuscular injection of penicillin and occasionally following oral administration. However, in many instances previous local applications of the drug have been the most likely cause of sensitization.

A series of 22 cases of patients with penicillin-sensitivity reactions which fit rather closely the clinical description of delayed serum sickness is here reported.

## REPORT OF CASES

*Age Incidence.*—The oldest patient was 58 years old; the youngest was 3 years old. The age distribution is presented in the following tabulation:

| Age, Yr. | No. |
|---|---|
| Under 10 | 2 |
| 10 to 19 | 0 |
| 20 to 29 | 6 |
| 30 to 39 | 4 |
| 40 to 49 | 7 |
| 50 to 59 | 3 |
| Total | 22 |

*Sex.*—Distribution as to sex was about equal, there being 12 men and 10 women.

*Time of Onset.*—The time from the last penicillin therapy until the onset of symptoms was 8 to 10 days for 6 patients and 12 to 14 days for 16 patients.

*Type of Penicillin.*—It was impossible to determine the type or brand of penicillin used. However, all therapy immediately previous to the onset of serum sickness was given intramuscularly.

*Previous Penicillin Therapy.*—Eighteen patients had previously, on more than one occasion, used penicillin locally in the form of either a salve, a lozenge, or eye drops. Four patients had previously received penicillin only intramuscularly. All patients had received at least some previous penicillin therapy within the last 12 months before the injection which resulted in the sensitivity reaction.

*Presenting Symptoms.*—In all patients pruritus associated with urticarial lesions was the first complaint. This began as a simple urticarial type of penicillin sensitivity. However, in 72 hours the full clinical picture presented itself in all patients.

*Cutaneous Lesions.*—Following simple urticarial lesions, angioneurotic edema of the hands, feet, and face developed in all patients by the second day. This was severe enough in 12 patients to close the eyes and make impossible the use of the fingers and the feet. The episode was dramatic enough to cause much apprehension in all patients. In the other 10 patients the edema was milder but enough to cause discomfort in walking and in use of the hands. The small urticarial lesions progressed to giant-sized lesions that were less transient. Pruritus was extremely severe. In six patients typical hemorrhagic bullous iris lesions of erythema multiforme

3. Beerman, H.: Drug Eruptions: A Survey of Recent Literature, Am. J. M. Sc. **218**:446, 1949.

4. von Pirquet, C. F., and Schick, B.: Die Serum Krankheit, Leipzig, F. Deuticke, 1905.

5. Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1951.

6. Longscope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, Medicine **22**:251, 1943.

developed. In one patient conjunctivitis resulted. This was a patient with a history of previous use of penicillin eye drops. Seven patients had severely sore, red, and swollen throats. These were patients with previous histories of the use of penicillin lozenges. Difficulty in breathing resulting from urticarial lesions of the larynx developed in only one patient.

*Temperature.*—Temperature ranged from 99 to 105 F. In most instances it ranged from 99 to 101 F. In only three patients did it pass 103 F. The temperature during the first days of the acute phase was the sustained type usually found in patients with drug fevers.

*Polyarthritis.*—Transitory pain and swelling of the joints of the extremities were present in all patients. In only one instance were these symptoms severe. In this patient an acute arthritis of the hip developed. Roentgenograms of the joint showed no abnormality, but traction for five days with added sedation of meperidine (demerol®) hydrochloride was necessary.

*Gastrointestinal Symptoms.*—There were no symptoms of nausea and vomiting, but, because of sore throat, in some patients anorexia was marked. Fluids were well tolerated.

*Psychogenic Symptoms.*—Apprehension was marked in all patients. Malaise was marked and often persisted long after the acute phase.

*Laboratory Findings.*—White blood cells counts were done for 12 patients, and all were above 10,500. The highest was 16,800. Repeated urinalysis in these 12 patients were normal except in one case. In this patient with the most severe reaction a temperature of 105 F. was maintained for four days, and there appeared 5 to 10 red blood cells and two to four fine granular casts, with albumin (3+). This condition persisted for only one week. Hemoglobin in all 12 patients was above 80% at the onset of illness. In one week nine of the patients had each lost 1 gm. of hemoglobin. One patient lost 2 gm. of hemoglobin in one week. The patient with the most severe condition mentioned above lost 5 gm. of hemoglobin in one week.

*Therapy.*—Ten patients were seen from one to four weeks after the onset of the disease. This group still had symptoms present in either severe or moderate form and were still incapacitated. They had all been under medical treatment, consisting of administration of antihistamines, epinephrine (adrenalin®), ephedrine, and sedation with either meperidine hydrochloride or one of the barbitals. None of this group had had bed rest. Two had received courses of cortisone parenterally.

Twelve patients were seen within 48 hours from the time of the onset of first symptoms. However, at the time they were first seen they all had the typical picture of serum sickness.

For all patients a routine similar to that used in treatment of acute erythema multiforme was prescribed, with complete bed rest. Fluids were forced to 3,000 cc. a day. Sodium salicylates were given to the extent of tolerance. A 10% chloral hydrate solution was used for sedation. Chlorprophenpyridamine ("chlor-trimeton") maleate, 4 mg. four times a day, was also given.

*Duration of the Disease.*—All patients who were seen in the first 48 hours and given bed rest and the above treatment routine had completely recovered in five to six days. There were no relapses. The remaining 10 patients had a slower recovery, varying in time from two to eight weeks. Relapse occurred only if patients were up and active before all lesions and symptoms had disappeared.

## COMMENT

The 22 patients in this study follow the usual coarse expected in a serum-sickness-like reaction. However, as typical of drug reactions, they are more protean than may be expected in true serum sickness. This may be due to the fact that the antigen-antibody combinations resulting from commercial penicillin lack permanence and are more readily reversible than is the case in reactions following sensitization with true proteins. It is becoming more apparent with more experience and investigation that the damage produced may not be a transient change as previously thought. The production of hemorrhagic iris-like lesions that are considered part of the erythema-multiforme picture is certainly clinical evidence for this point of view. Even more convincing is the sequela noted in one patient of an erythema nodosum persisting for eight months following the serum sickness reaction.

It is significant that 18 of 22 patients had previously used penicillin locally.

The loss of hemoglobin in all patients certainly is indicative of changes in the hematopoietic system. The mechanism of the loss of hemoglobin is not understood.

Despite the fact that infants and children of this present era have been more exposed to repeated antibiotic therapy than older persons, there are few reports of reactions of this sort in the very young. However, it is interesting to note the occurrence of this syndrome in two children, one 3 years old and the other 4 years old.

Simple antihistamine and epinephrine therapy is not adequate to control these reactions.[7] On the other hand, care necessitating hospitalization or expensive therapy is not necessary for recovery. The most important features of treatment for early remission without relapse are early institution of bed rest and simple symptomatic therapy.

## CONCLUSIONS

The cases of 22 patients with delayed serum-sickness-like reaction to penicillin have been reported.

Eighteen of the patients had previously used penicillin locally.

It is suggested that there may be damage resulting from these reactions that is more than a transient syndrome.

Therapy should be instituted early and should include bed rest until the acute phase has completely subsided.

18 Montague St.

7. Zussman, B. M.: Severe Serum Sickness Type of Penicillin Reaction: Failure of Antihistamine Therapy, Ann. Allergy **8**:751-753, 1950. Hansel, F. K.: Penicillin Sensitivity, ibid. **7**:619 and 624, 1949.

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# USE OF PLASTIC BOTTLES FOR DERMATOLOGICAL PHARMACEUTICALS

ORLANDO CANIZARES, M.D.
NEW YORK

Recently, plastic or polyethylene bottles have been widely used by cosmetic manufacturers and pharmaceutical companies. They have the advantage of being unbreakable and light in weight. The "spray-type" bottle gives a fine, vaporized or jet application, depending upon the position in which it is held and the consistency of the substance used.

On certain occasions in dermatological practice, it may be advantageous to use this type of packaging. This is particularly desirable in the case of the discriminating patient.

The usual watery solutions may be easily applied with the spray-type bottle. It delivers a fine mist which may be directed toward the desired area. This simplifies the application, for no cotton or gauze is needed. Shake lotions may also be applied with the spray-type container, but instead of a fine mist a direct jet is obtained, which may be directed toward the affected area. The application of this type of preparation requires a little practice. Heavier emulsions cannot be applied with this type of bottle. Dusting powders, however, if finely spun, may be applied with the spray-type plastic bottle. Its use facilitates the application of the powder to certain parts of the body, such as the perineum. By this means a fine and evenly distributed application may be secured.

In order to obtain satisfactory results, the dermatologist should become acquainted with the behavior of his prescriptions in plastic bottles. In my experience the commonly prescribed dermatological preparations do not affect this type of packaging.

The use of the plastic bottles simplifies the application of the medicament and lends a refined touch which, in my experience, is appreciated by the patient.

3 E. 69th St.

# Correspondence

## FIXED DRUG ERUPTION AND EPIDIDYMITIS DUE TO ANTIPYRINE

*To the Editor:*—In the August, 1951, issue of the ARCHIVES, there is a report by McCulloch and Zeligman of a case of fixed drug eruption and an extracutaneous effect, an epididymitis, due to the ingestion of antipyrine (**64**:198). The authors state that they were unable to find in the literature any reports of fixed extracutaneous effects from drugs, other than those reported by J. Jadassohn and by Haber, which they cite.

To my knowledge a few similar reports exist in the literature. I have reported a case of fixed eruption with an extracutaneous effect due to oxophenarsine hydrochloride (mapharsen®). The eruption, which was of the erythematous type, appeared on both palms and in the left toe 5 to 10 minutes after an injection and disappeared within three days, leaving no pigmentation. The extracutaneous effect consisted of severe, sharp pain in the upper jaw that appeared 10 to 20 seconds after an injection and lasted 5 to 10 minutes. Both effects recurred in identical manner after each of six injections of oxophenarsine hydrochloride (Mendelsohn, H. V.: Fixed Eruption with an Extracutaneous Manifestation Due to Mapharsen: Report of a Case, ARCH. DERMAT. & SYPH. **41**:509 [March] 1940). Bargues noted motor and sensory disturbances of various nerves and swellings of the jaw, recurring with each injection of neoarsphenamine (Bargues, M.: Crises nitritoides localisées, *Bull. Soc. franç. dermat. et syph.* **28**:244 [May 17] 1921). Astrachan and Sharp studied five patients with fixed eruptions, two of whom complained of headaches and "soreness" of both eyes and swelling and itching of the eyelids. Readministration of oxophenarsine resulted in the same subjective and objective symptoms (Astrachan, G. D., and Sharp, E. A.: The Value of Administration of Liver in Patients Intolerant to Arsenicals, *J. Invest. Dermat.* **1**:427 [Dec.] 1938).

I have not reviewed the literature on this subject recently. The above references are those which I found in the literature at the time I submitted my report.

H. VICTOR MENDELSOHN, M.D., New York.

# Society Transactions

## CHICAGO DERMATOLOGICAL SOCIETY

**Stephen Rothman, M.D., *President***

**James R. Webster, M.D., *Secretary***

***April 18, 1951***

**Panniculitis (Weber-Christian Disease?).** Presented by DR. JAMES H. MITCHELL and (by invitation) DR. HEYWORTH SANFORD.

G. W., an 8½-month-old child, was admitted to Presbyterian Hospital on April 9, 1951, with the presenting complaints of "skin eruption and intermittent fever of 100 to 102 F." for two and a half months.

The first lesions were noted by the parent on the lower abdomen. These were described as being the size of a quarter and gave the skin involved the appearance of light red in the center and purple toward the periphery. Since that time these lesions have appeared on other parts of the body in the following sequence: flank, upper chest, lower back, chin, right thigh, legs, and elbows.

The general picture of the patient has become one of lethargy and irritability, with intermittent temperature elevation, as high as 104 F.

Various forms of treatment have been employed, which to the present have proved ineffective. These have included two courses of penicillin administration, both in a period of more than 10 days, sulfadiazine therapy for a period of 11 days, and aureomycin treatment for 11 days. Most recently corticotropin (ACTH; 15 mg. every six hours) and, as of April 17, 1951, chloramphenicol (chloromycetin®; 250 mg. every six hours) were used.

The positive physical findings are as follows: The patient is an acutely, chronically ill, 8½-month-old white boy, who is lethargic but irritable on any movement. Multiple, indurated, irregular lesions are present which vary in color from moderate hyperemia to dark purple. Induration is more marked in the center, with central involution; the lesions are neither tender nor hot. The areas involved are the anterior neck and chin bilaterally, outer face, upper chest, lower back, and both upper thighs, elbows, and ankles. The heart shows a Grade I apical systolic murmur. The liver is 4 cm. below the costal margin. Edema of the right lower extremity is present. Lymph nodes are not enlarged.

Biopsy specimens taken from the left flank at Michael Reese Hospital showed characteristics compatible with Weber-Christian disease. Those taken from the left inguinal region at Presbyterian Hospital showed nonspecific fat and inflammation.

Blood studies on April 9, 1951, disclosed 9 gm. of hemoglobin per 100 cc., 3,540,000 red blood cells, and 3,300 white blood cells. Those made on April 16 revealed 4.47 gm. of hemoglobin per 100 cc., 4,470,000 red blood cells, and 2,800 white blood cells, with a differential count of 80% polymorphonuclear leucocytes and 20% lymphocytes. After centrifugation for five minutes of the blood specimen obtained on April 17, the serum appeared very milky. A determination for fat content will be done. Bone marrow revealed production of both red and white blood cells, with a ratio of red blood cells to white blood cells of 2:1. Cholesterol content of the blood measured 124 mg. per 100 cc. The urine showed a 1+ reaction for albumin. Microscopic examination revealed nothing abnormal. A roentgenogram showed the long bones to be normal. Cultures of material from the throat showed Streptococcus viridans (4+) and hemolytic Streptococcus pyogenes (4+). A culture of the blood was negative for pathogenic organisms. Tissue from the biopsy site grew anaerobic streptococci on chocolate proteose agar. The growth was transferred to broth, and then to a blood agar plate. Str. viridans was produced in green colonies, which became slightly hemolytic when plates stood at room temperature for several days. The Str. viridans isolated showed 4+ sensitivity to sulfadiazine, chloramphenicol (chloromycetin®), and aureomycin.

Three blood transfusions each of 250 cc. were given.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This is a unique case. Weber-Christian disease was originally described as an acute, inflammatory disease with fever and with fat necrosis due to invasion of the fat with polymorphonuclear leucocytes. The section from this case reveals panniculitis with infiltrate of lymphocytes and is not characteristic of Weber-Christian disease. The possibility of a lymphocytic or a hemorrhagic diathesis of some form should be considered.

DR. MARCUS R. CARO: I am as much at a loss as Dr. Montgomery, and I do not know what type of panniculitis it is. It might be well to have a complete blood work-up to see if some form of lymphoblastoma is present.

DR. HERBERT RATTNER: This baby was presented at a meeting of the Michael Reese Pediatric Department about a month ago. It was stated by the pediatrician that not only was the condition an unusual example of Weber-Christian disease but the baby was the second youngest patient on record with the disease.

**Morphea-Like Basal-Cell Carcinoma.** Presented by DR. RICHARD B. STOUGHTON (by invitation).

I. H., a 51-year-old white woman, has noticed a "scar" on the right cheek as long as she can remember. However, this "scar" has very gradually increased in size over many years but so slowly that the growth has been barely noticeable. There has been no ulceration, crusting, or bleeding from the lesion.

Physical examination gave essentially normal results except for a 2- by 1.5-cm. firm, yellowish infiltration with overlying telangiectasia on the right cheek. There is no elevation at the borders. Laboratory tests on the urine showed normal excretion of phenolsulfonphthalein. There was no reaction for albumin, and microscopic examination showed no abnormalities. Blood studies disclosed 5,100 white blood cells, and 15.4 gm. of hemoglobin per 100 cc. The Kahn reaction was negative. A microroentgenogram of the chest was normal.

A biopsy section of the lesion on the right cheek is presented. The epidermis is atrophic. There is collagen degeneration of the upper cutis. Throughout the corium there are scattered elongated strands and islands of hyperchromic basal cells which are surrounded by dense, somewhat sclerotic connective tissue.

DISCUSSION

DR. MARCUS R. CARO: I think that this case is a perfect example of morphea-like epithelioma on both clinical and histopathological grounds. The location on the face speaks against morphea. The morphea-like clinical appearance is produced by the presence of long strands of basal cells which are separated from each other by dense fibrous connective tissue. The fibrosis is not secondary to ulceration, because in most of the cases I have seen there was no ulceration and the dense fibrosis was present. It is unfortunate that these patients are generally not seen by the dermatologist for many years and that their condition is not properly diagnosed and treated. I recently saw a patient with such a lesion, which was treated for the past few months with sulfathiazole ointment.

DR. STEPHEN ROTHMAN: This patient insists that she has had some lesion in this spot since earliest youth, possibly since birth. Is anything known about predisposing lesions (keratotic nevi, scars, etc.) in cases of morphea-like basal-cell carcinoma?

DR. HENRY E. MICHELSON, Minneapolis: Dr. Caro, Dr. Howell, and I have discussed these morphea-like epitheliomas before. The condition is a morphologic entity. One probably sees many epitheliomas that are similar to the morphea-like type but are not, strictly speaking, of that variety. In Dr. Caro's paper he mentioned that some of the lesions he examined turned out to be squamous-cell cancer. It would require most careful comparison between the morphology and the miscroscopic picture to be certain that those lesions which showed squamous-cell cancer met the requirements which would classify the lesion as morphea-like. There are so many cancers of the skin with fibrosis; that, of course, modifies the external appearance.

DR. MARCUS R. CARO: In answer to Dr. Rothman's question, it is possible that some of these lesions may begin as benign cystic epithelioma and undergo subsequent malignant changes.

DR. RICHARD B. STOUGHTON (by invitation): I should like to bring up one point that was mentioned in the discussion on the paper by Dr. Caro. Morphea-like basal-cell carcinomas, when exposed to the Wood light, reveal an altered fluorescence which extends beyond the margins of the lesion as defined under natural light. I found this to be true in my patient.

**Case for Diagnosis: Histoplasmosis? Tuberculosis Cutis Lichenoides?** Presented by DR. FRANCIS C. PRUNTY, Urbana, Ill.

P. A. M., a girl 6½ years of age, had no family history of tuberculosis. The past history was as follows: Delivery was normal. She had occasional upper respiratory infections during the first two years of life. In May, 1947, the child had what was diagnosed as atypical pneumonia. At this time, a chest roentgenogram showed marked right hilar enlargement. At about that time, the child exhibited what was apparently erythema nodosum. In June, 1947, there was considerable consolidation of the base of the right lung. A Vollmer tuberculin test done then was said to have had a positive reaction. Findings at the right base had changed little by September, 1947. In March, 1948, the chest roentgenogram was reported as showing considerable resolution of the previously noted shadow in the right base. During this period, the child's condition had been diagnosed as primary tuberculosis. The last chest roentgenogram, made in January, 1951, showed prominence of the right side of the upper mediastinum.

The lichenoid papillary eruption which the child presents was first noted by the mother when the child was 2½ years old. There has been a gradual increase in the number of lesions and groups of lesions. These were first noted on the dorsum of the foot and the vulva and have now become widespread. A course of treatment with calciferol caused no change in the picture. In February, 1951, tests with first-strength, and second-strength tuberculin (purified protein derivative) gave negative reactions. A histoplasmin test was then done with 1:1,000 dilution and showed a strongly positive reaction. About a month later, this test was repeated to eliminate any possibility of an error, and the reaction was again very strongly positive. The tuberculin tests were also repeated and gave negative reactions. Results of a recent urinalysis were entirely normal, and the latest blood count showed a sedimentation rate of 11 mm. in 45 minutes, a hemoglobin concentration of 13.8 gm., 4,430,000 erythrocytes, 6,250 leucocytes, 48% neutrophiles, and 52% lymphocytes. A biopsy section from a lesion on the abdomen is presented.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I cannot offer a positive diagnosis. I considered lichen planus, lichen nitidus, or lichen scrofulosus and also thought of a lichenoid eruption as part of an eczema. I felt we could rule out lichen planus by the appearance of the lesions, and the Mantoux reaction being negative pretty much excludes lichen scrofulosus. The microscopic section could be interpreted as lichen nitidus. That seemed to me to be the best diagnosis.

DR. MICHAEL H. EBERT: This is an interesting case. Although the lesions resembled lichen scrofulosus, the tuberculin reaction was negative. It is possible that this "id" type of lesion may be produced by histoplasmosis. As I remember the history, the roentgenograms showed hilar nodes and some infiltrate in the lung. It is also true that the reaction to the Vollmer histoplasmin test was positive. So many times in roentgenologic examination hilar nodes and areas of calcification are present without any evidence of tuberculosis, but with a positive reaction to a histoplasmin test. Subclinical histoplasmosis has been postulated as the cause of such lung changes.

DR. STEPHEN ROTHMAN: In my experience the reaction to the Mantoux tuberculin test is always positive in tuberculosis cutis lichenoides down to dilutions of 1:100,000 or even 1:1,000,000. If this is "histoplasmid," it is probably the first observation of this kind.

DR. ADOLPH ROSTENBERG JR.: One might get some immunologic evidence showing whether this disease is or is not histoplasmosis by using the Moro contrast test. The test consists of rubbing a tuberculin-containing ointment into a suspicious lesion and into the surrounding normal skin. If the lesion yields a greater reaction than the normal skin, it is tuberculous. In this case, the problem is whether the eruption is one caused by histoplasmosis. One could incorporate histoplasmin in an ointment and rub it into the lesion and the adjacent skin. If the reaction were greater in the affected area, it would be in favor of the diagnosis of histoplasmosis.

DR. R. E. JENKINS (by invitation), Indianapolis: Though I am not directly concerned with the work, I am in touch with case studies on histoplasmosis made at the Indiana University Medical Center over 10 or 11 years. The group there has collected 8 or 9 proved cases in that time and has also collected verified reports of 25 or 30 cases in the state of Indiana. They have felt that many cases of unexplained fever, splenomegaly, and anemia can be found to be histoplasmosis if careful studies are done.

DR. F. C. PRUNTY, Urbana, Ill.: Dr. Ebert mentioned a point I had in mind. This child's condition was diagnosed as pulmonary tuberculosis and erythema nodosum at the age of 2½ or 3 years. The eruption as we see it today began to appear in small areas on the vulva and on one foot. It has progressed very gradually. We have seen so many cases in which there was an eruption classified in the tuberculosis cutis group with a negative tuberculin reaction and very little to go on except the clinical or histological picture, or both. This child had a negative reaction to the tuberculin test on two occasions, and also a strongly positive histoplasmin reaction on two occasions. I wonder if this could be an "id" to histoplasmosis. I will be happy to follow out Dr. Rostenberg's suggestion and report further. There are considerable hilar calcification and markings in the child's right chest. She was later operated upon and found to have tuberculous peritonitis.

**Urticaria Pigmentosa**. Presented by DR. HAROLD SHELLOW.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I accept the diagnosis of urticaria pigmentosa. Dr. Klemperer in his discussion in a recent symposium recognized differences among lupus erythematosus, dermatomyositis, and scleroderma but still grouped them under the very broad and loose concept of collagenous diseases. I wish to bring out the concept that urticaria pigmentosa is also probably a true collagenous disease. It is well known that mast cells are present in urticaria pigmentosa and that they are concerned with the production of heparin. Asboe-Hansen, however, has shown that they contain hyaluronic acid and mucopolysaccharides. In two cases of urticaria pigmentosa in which the specimens had been fixed in dehydrated alcohol, I found positive reactions to mucin with mucicarmine stain, toluidine blue stain, Hotchkiss, and McManus stains. The granules in the mast cells were brought out with these different stains. One is not dealing, however, with just mucopolysaccharides but with glycoproteins also.

DR. RICHARD B. STOUGHTON (by invitation): Hotchkiss or McManus stains will show up almost all the polysaccharides of the skin and those in the mast cells very well. One finds a considerable number of mast cells in a variety of skin lesions. We have noted a considerable number to be present in lichen sclerosus et atrophicus, in poikiloderma atrophicans, and in many different collagenous diseases.

**Porphyria with Bullous Lesions.** Presented by DR. OLIVER S. ORMSBY and DR. MICHAEL H. EBERT.

H. G., a white man, aged 52, born in Norway, has noticed in the past six months that small bullae have appeared on the dorsa of the hands and fingers at the sites of slight trauma. When a bulla ruptures, the resultant erosion crusts over and heals slowly, leaving in some instances a shallow scar. He has been under observation for two and one-half months. On each visit one or more small bullae were observed, appearing on normal skin. He states that for the last two summers small, superficial vesicles have appeared on the sides of his fingers after working in his garden. Nothing of significance was discovered in his family history. The patient is of a nervous, high-strung temperament. He has suffered from insomnia as long as he can remember. He has taken a large amount of phenobarbital and other sedatives for the insomnia. About eight years ago, while under heavy business pressure, he became extremely nervous and had to stop work for two weeks. He gives no history of abdominal pain or gastrointestinal upsets. He has had no headaches.

A 24-hour specimen of urine was a light, sherry red color. The urine fluoresced a light pink in the Wood light. The Watson-Schwartz test for porphobilinogen gave a negative reaction on several occasions.

An aliquot portion of a 24-hour specimen of urine was sent to Dr. Samuel L. Nesbitt, at the Veterans Administration Hospital, Minneapolis. Dr. Nesbitt reported that there were 1,027 μ of coproporphyrin and 8,632 μ of uroporphyrin excreted in 24 hours. The uroporphyrin was present as the zinc metal complex. He also found the reaction to the porphobilinogen test negative.

Liver-function tests were done. The prothrombin time was normal. The results of the direct van den Bergh, the cephalin flocculation, and the thymol turbidity tests were all within normal limits.

DISCUSSION

DR. MICHAEL H. EBERT: I had hoped that Dr. Brunsting might be present to discuss this interesting group of diseases. He stimulated my interest in them some years ago. Porphyria is an inherited defect in the pyrrole metabolism. It is manifested by the appearance of abnormal amounts of uroporphyrin in the urine. This may be intermittent. The disease may remain latent unless precipitated by the abnormal use of alcohol, phenobarbital, or other toxic substances. The gastrointestinal manifestations, as well as the neurological changes, are very obscure unless porphyria is thought of and a urine examination for uroporphyrin made.

The urine of this patient showed very beautifully the characteristic fluorescence under the Wood light. Ordinarily uroporphyrin may be present, as well as its colorless precursor porphobilinogen. In this case porphobilinogen was not present. Later the uroporphyrin was present as a zinc salt. In this connection it is interesting to note that a great deal of work has been done at Harvard Medical School on the significance of zinc in blood dyscrasias. It has been found in abnormal amounts in pernicious anemia. When vitamin $B_{12}$ therapy is used to improve this condition, the zinc content does not return to normal.

Another interesting feature of the present case was that we elicited a history of vague neurological manifestations when the porphyria was once recognized. He has complained of insomnia ever since childhood and has used large amounts of phenobarbital and other drugs to control it. He also gives a history of what was termed a "nervous breakdown" on two occasions.

Porphyria is not difficult to diagnose if one constantly keeps it in mind and makes the proper examinations.

**Nevoxanthoendothelioma in a Male Infant.** Presented by DR. JAMES H. MITCHELL and (by invitation) DR. ROBERT M. GOODWIN, Springfield, Ill.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I formerly believed that nevoxanthoendothelioma was different from juvenile xanthoma in that the lesions of nevoxanthoendothelioma disappeared spontaneously, and there was no disturbance of blood lipids or any familial history or evidence of cardiovascular disease. This, however, no longer holds true, as Beerman has pointed out in an excellent review of the subject of xanthomas (*M. Clin. North America* **35**:433 [March] 1951), and he has cited several cases in which nevoxanthoendothelioma has persisted and has not involuted.

**Erythroplasia of Queyrat (?).** Presented by DR. JAMES R. WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI.

DISCUSSION

DR. S. J. ZAKON: On close inspection of the lesion I believe that this man has an early carcinoma of the penis. In a recent issue of the *British Medical Journal* (**2**:1433 [Dec. 24] 1949), Dr. Douglas Gairdner discussed the problem of circumcision and penile cancer. About 300 to 400 males die in the United States annually of carcinoma of the penis. (These figures are taken from the reports of the Vital Statistics Division, United States Bureau of the Census.) It is an accepted fact that cancer of the penis does not occur among Jews. Circumcision in infancy definitely prevents carcinoma of the penis, yet the advisability of routine circumcision is still a subject of controversy. I ask in earnestness, is the foreskin worth that much? Why should not we dermatologists who see penile carcinoma advocate routine neonatal circumcision?

DR. ROBERT M. GOODWIN (by invitation), Springfield, Ill.: Four years ago I saw a patient with very definite epidermal cancer of the coronal sulcus. He was treated at the Veterans Administration Hospital, Hines, Ill., with x-rays only. I see him regularly, and he is quite well.

DR. THEODORE CORNBLEET: Moh's chemosurgical procedure might spare this patient the penile amputation now intended.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This patient with erythroplasia has not had circumcision. We see many men at Mayo Clinic who have intense irritation beneath the foreskin, but, if simple circumcision is performed, the majority of these clear up. If irritation persists, then one can anticipate development of leucoplakia and then epithelioma *in situ*. It is well known that practically all Jews are circumcised soon after birth, and the same is true of certain other Asiatic races; carcinoma of the penis does not occur in Jews who have been circumcised. I do believe that in these cases of moist leucoplakia or erythroplasia of Queyrat one should do a circumcision and then wait two or three months before considering amputation unless there is clinical or pathologic evidence of a frank carcinoma.

**Pseudoxanthoma Elasticum Since Early Childhood.** Presented by DR. S. W. BECKER.

**Pseudoxanthoma Elasticum Without Angioid Streaks of the Retina.** Presented by DR. EDWARD A. OLIVER and staff.

**Rat-Mite Dermatitis.** Presented by DR. PAUL BOSWELL.

**Necrobiosis Lipoidica Diabeticorum Occurring in an Old Abdominal Scar.** Presented by DR. ALBERT SLEPYAN, Highland Park, Ill., DR. S. KAPLAN, and (by invitation) DR. S. M. MESIROW.

**Pemphigus Erythematodes.** Presented by DR. H. R. FOERSTER, Milwaukee, and DR. D. M. RUCH, Milwaukee.

**Case of Pemphigus (Erythematodes?).** Presented by DR. MICHAEL H. EBERT and (by invitation) DR. ALLEN S. PEARL JR., Oak Park, Ill.

**Case of Pseudopelade (Lupus Erythematosus?).** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. STEFAN BIELINSKI.

**Alopecia, Striae Distensae, and Macular Atrophy in a Patient with Endocrine Dysfunction: Thyroid(?) Pituitary(?).** Presented by DR. JAMES R. WEBSTER.

**Circumscribed Scleroderma and Hypothyroidism.** Presented by DR. A. M. BUCHHOLZ.

**Monilial Granuloma Simultaneously Treated with Corticotropin and with Fungicides.** Presented by DR. CALVIN J. DILLAHA (by invitation).

**Pityriasis Rubra Pilaris.** Presented by DR. MALCOLM C. SPENCER, Danville, Ill.

**Case for Diagnosis: Lymphoblastoma? Cutaneous Nodules?** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. LYDIA C. MARSHAK.

**Lymphosarcoma on Leg.** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

**Purpura Annularis Telangiectodes (?).** Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

**Erythema Multiforme Associated with Rheumatic Fever.** Presented by DR. MICHAEL H. EBERT, DR. JAMES R. WEBSTER, and (by invitation) DR. STEFAN BIELINSKI.

**Sarcoidosis with Hereditary Leptocytosis (Thallassemia) Associated with Leg Ulcers.** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

**Palmar and Plantar Keratoderma with Fissuring Due to Psoriasis.** Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

**Psoriasis of the Palms.** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

**Stephen Rothman, M.D., *President***

**James R. Webster, M.D., *Secretary***

***Oct. 17, 1951***

**Cylindroma (Turban Tumor) Limited to the Arms.** Presented by DR. E. M. SMITH.

Mrs. F. B., a white woman aged 48, has a patch of noninflammatory cutaneous and subcutaneous nodules above the deltoid area of the left arm.

The patient states that the lesion began 10 years ago as a "broken vein." The lesion was stationary until it began to grow about one year ago. During the last three months the lesion has not increased very much in size.

Examination shows a group of noninflammatory nodules, some of which are a little tender to the touch. The lesions are grouped in a band about 1 in. (2.5 cm.) wide and 2 in. (5 cm.) long.

Biopsy shows a cylindromal type of lesion which is often described as a turban tumor.

DISCUSSION

DR. OLIVER S. ORMSBY: This case is a very interesting one to me for the reason that all the patients I have seen with this condition had the lesions in the scalp. In this patient they

were limited to the arm. I have no doubt that the diagnosis is correct, because sections were examined and confirmed the diagnosis.

Dr. M. R. Caro: I agree with the diagnosis of cylindroma, for the section was diagnostic of that disorder. I have never before, however, seen the lesions in this location.

Dr. Hamilton Montgomery, Rochester, Minn.: I have been seeing increasing numbers of patients with a solitary cylindroma. The lesion may occur on any part of the body. It is interesting, too, that cylindroma often does not appear until the later decades of life. In other words, one is dealing with a delayed nevus. The term nevus epitheliomatocylindromatosus is preferable to the term cylindroma but is much too awkward to say. It is significant that these cylindromas of the skin have a hyaline-like membrane, palisade arrangement of the strands of the cells and hyaline-like changes in the centers of the nests of cells. They are constantly being confused with sweat-gland tumors; however, as Gans pointed out many years ago, they do not connect up with the sweat glands, but they do connect up with hair follicles, and one can see transitions between cylindroma and epithelioma adenoides cysticum. These lesions are benign and are not even as invasive or destructive as ordinary basal-cell epitheliomas are.

**Tinea Capitis Due to Microsporum Fulvum (Gypseum).** Presented by Dr. I. M. Felsher.

DISCUSSION

Dr. John E. Dalton, Indianapolis: Our staff has collected about 20 cases of this entity. The first was in a pharmaceutical worker who was referred for a ruling on whether the condition could be work-associated. She presented a single self-limited patch with peripheral vesiculation of the medial surface of the left calf, and, for that reason, cultures were made on Sabouraud's medium. The tube grew Microsporum fulvum, and the case was ruled nonoccupational. In all our patients who presented a scalp involvement with this strain of fungus kerion developed, and thus cure could be attained by topical application of fungicides. However, the hair in these patches failed either completely or partially to regrow. Furthermore, if one relies solely on positive Wood-light fluorescence for picking out suspected cases of tinea capitis, one will miss this group. In our paper and in most other reports on this subject, the absence of fluorescence in these cases has been noted. Several physicians who visited our exhibit on Microsporum fulvum at the meeting of the American Medical Association told us of proved cases in their particular practices which they had not reported. Thus, it seems that this entity is not as rare as one might assume from the literature.

Dr. J. B. Howell, Dallas, Texas: My colleagues and I see an occasional case of Microsporum fulvum (gypseum). I should like to emphasize that the infected hairs often do not fluoresce and to point out that it is a very common cause of kerion.

Dr. Irene Neuhauser: One more important point should be emphasized. In the early stage, Microsporum fulvum infection may be confused with favus. In addition to absence of fluorescence, spores may be found within the hairs. Of course, the organism can be readily identified by culture. I saw some of the hairs from one of Dr. James H. Mitchell's patients, and the hairs were so full of spores that some of them had ruptured.

Dr. I. M. Felsher: The patient was presented because tinea capitis due to Microsporum fulvum (gypseum) is still uncommon in the Chicago area, though more reports of such cases have been coming in recently from different parts of the country. The organism was first isolated by Uriburu in Argentina in 1909, with reports later from Hungary and Germany and still later from the United States. From 1930 to 1940 there was a lull in reporting the finding of this organism. About 1940 Moore, of St. Louis, reported one case. In the survey Dr. T. Benedek and I made in Chicago in 1940 and 1941, we found 3 cases of tinea capitis caused by Microsporum fulvum (gypseum) in 140 patients. Later in Philadelphia 6 instances of Microsporum fulvum (gypseum) infection were found in 150 patients. Lewis and Hopper recorded the finding of several cases in 1948. More recently, reports of Microsporum fulvum (gypseum) infections have come from Texas, the District of Columbia, Indiana, Kentucky, and California. Wilson and Plunkett raised the question whether Microsporum fulvum and Microsporum gypseum were different organisms and thus accounted for the absence of fluorescence in some instances and its presence in others. The majority of the lesions of the scalp reported

did not show any fluorescence under the Wood light. I had the opportunity in the last few months to see three patients with tinea capitis caused by Microsporum fulvum (gypseum), and none showed any fluorescence. The scalps of two patients cleared completely. The present case is the last of the three.

It is interesting to note the evolution in Chicago in the epidemiology and etiology of the organisms causing tinea capitis. From 1944 to about 1946 the predominating causative organism was Microsporum audouini, with a small number of cases caused by Microsporum lanosum and a very few by Trichophyton. Most of the patients had involvement in large areas of the scalp, and the hairs gave a bright green fluorescence. There were relatively few cases of kerion. The disease was recalcitrant to local therapy available at that time and lasted for many years. We had to resort to x-ray epilation for final cure. From 1946 to the present we have seen milder forms of the disease with fewer and smaller lesions on the scalp that responded better to local therapy. We have also seen in this period more instances of kerion caused even by Microsporum audouini. In instances in which no kerion was present at the beginning of therapy the therapeutic measures seemed to induce kerion or kerion-like formation. When this occurred, the prognosis became more favorable. Quite recently, we have begun to see in Illinois, Kentucky, and Indiana the occurrence of tinea capitis caused by Microsporum fulvum.

**Granuloma Annulare.** Presented by DR. A. L. GOLDBERG and (by invitation) DR. B. J. PASS.

J. H., a 9-year-old white girl, was first seen at the Dermatology Clinic of the Northwestern University Medical School on Aug. 7, 1951, with an eruption of six months' duration on the legs and thighs, the dorsa of the hands, and the extensor surfaces of the arms and elbows. The mother stated that the eruption began on the legs and gradually spread to involve the other areas. There are numerous discrete, reddish-brown, annular, nodular lesions, about 0.5 to 4 cm. in diameter, with raised borders consisting of small papules 1 to 3 mm. in diameter. All the lesions are infiltrated and sharply demarcated, and the larger ones have a slight central depression.

The physical examination and serologic tests of the blood gave normal results.

The urinalysis disclosed no abnormality. The blood studies revealed 12.8 gm. of hemoglobin per 100 cc., a cell pack of 40 cc. per 1,000 cc., and 7,600 white blood cells per cubic millimeter. A roentgenogram of the chest was reported as showing no abnormalities.

After a biopsy of one of the lesions, others appeared to regress slightly. The histologic picture showed changes compatible with granuloma annulare.

**Erythema Elevatum Diutinum.** Presented by DR. MALCOLM C. SPENCER, Danville.

DISCUSSION ON PRECEDING TWO CASES

DR. H. E. MICHELSON, Minneapolis: Gougerot recently divided cases of granuloma annulare into three types: (1) those in which the clinical and microscopic diagnoses are beyond doubt; (2) those in which the clinical diagnosis is positive, but the microscopic picture is not corroborated, and (3) those in which the lesions are nondescript but the microscopic picture is characteristic of granuloma annulare.

As far as therapy is concerned, it is interesting to note that in this country dermatologists have given up the idea of a tuberculous origin and, therefore, have not followed an antituberculosis type of therapy. Vitamin $D_2$ treatment has been reported to be of great help. On the other hand, exacerbations from its use have been noted. I have used vitamin $D_2$ in a few patients and have seen striking improvement. I do feel, however, that no patient should be jeopardized by therapy in granuloma annulare because the disease itself amounts to so little.

With reference to erythema elevatum diutinum, Dr. Senear and I used to be greatly amazed at some of the candidates who came before the American Board of Dermatology and Syphilology when they discussed this disease so fluently. I believe I am familiar with the literature on the condition, and I do not know precisely what erythema elevatum diutinum is. I limit my concept of erythema multiforme to that of an acute disease. I look askance at a diagnosis of chronic erythema multiforme. I think in such instances one is dealing with a fixed type of eruption which may be due to many causes, but I do not believe it should be called erythema multiforme.

DR. S. M. BLUEFARB: I have seen only one case of erythema elevatum diutinum (ARCH. DERMAT. & SYPH. **42**:441 [Sept.] 1940), and it did not resemble the case presented today.

In erythema elevatum diutinum the lesions are flat, raised, and violaceous, with no central clearing, and usually occur in middle-aged or elderly men. The lesions are persistent. This patient is a young woman whose lesions consist of red nodules with central clearing. These lesions have faded and reappeared. Histologically this is not erythema elevatum diutinum, as the process is not acute in that there are no polymorphonuclear leucocytes. The exact status of erythema elevatum diutinum has never been fully clarified. At present some believe it is similar to the condition now called eosinophilic granuloma of the skin. Trimble (ARCH. DERMAT. & SYPH. **13**:383 [March] 1926) has reported the only case of erythema elevatum diutinum with autopsy. His patient died of lymphosarcoma.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Ormsby and I have a picture of Dr. Weidman's patient with erythema elevatum diutinum in our textbook; I have a slide from the case and have discussed with Dr. Weidman the differences that he brings out between erythema elevatum diutinum and granuloma annulare. He emphasizes that the histopathologic changes in erythema elevatum diutinum are distinctive and consist of an acute toxic periarteritis and peritelangiitis in the corium, with swelling of the capillary walls, hyaline changes, and migration of polymorphonuclear leucocytes through the walls. There is also hypertrophy of the epidermis. Dr. Spencer's patient did not show a histologic picture typical of erythema elevatum diutinum, but there were some changes suggesting such a diagnosis. The lesions did not show the picture of granuloma annulare. Dr. Weidman's case was associated with rheumatic disease, which ties erythema elevatum diutinum in with a picture of toxic erythema or an erythema multiforme type of reaction, which, in turn, ties in with what Dr. Michelson and Dr. Senear have said about this condition. I have seen three cases that I believe fit the rigid requirements of erythema elevatum diutinum; both clinically and histologically, I believe granuloma annulare to be something entirely different. Dr. Prunty and I in 1942 (Granuloma Annulare, ARCH. DERMAT. & SYPH. **46**:394-413 [Sept.] 1942) reported a study of 31 cases without any definite evidence to substantiate a tuberculous causation for granuloma annulare.

DR. MALCOM C. SPENCER, Danville: At no time has my patient been seriously ill as a result of her cutaneous problem. She has been, however, seriously ill as a result of treatment for this eruption. In 1948, it is reported that she had agranulocytosis, with a white blood cell count of 600, as a result of taking paraaminobenzoic acid (PABA) for a period of 25 days. When she was initially seen by Dr. J. Dudley Youman Jr., of Shreveport, La., the clinical impression was a toxic erythema. The biopsy specimen taken from the forearm at that time was interpreted by Dr. Fred Weidman as being characteristic of lupus erythematosus. I asked Dr. Weidman to review this biopsy specimen in view of the present clinical findings. He reported that he was unable to change his original opinion.

It should be pointed out that at the sites of the three biopsies made since she has been under my observation complete involution of the lesion has followed. It is of further interest that there has been appreciable clinical improvement during a period that she was taking regularly tripelennamine (pyribenzamine®) hydrochloride, 50 mg. four times daily, despite her failure to respond to adequate doses of corticotropin (ACTH).

**Benign Familial Pemphigus Improved with Aureomycin Therapy.** Presented by DR. THEODORE CORNBLEET.

**Pemphigus Vegetans Being Treated with Heparin.** Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

At the time of admission to the hospital the patient, a 63-year-old white man, presented vegetating, moist lesions of the opposing surfaces of the axillae and the genital area. On the chest wall, the neck, and the upper portion of the back there were many eroded areas and some flaccid bullae and vesicles. The entire erupted area was erythematous. There were scattered eroded and crusting lesions of the scalp and some small erosions of the buccal mucous membranes.

On laboratory studies results of urinalysis were normal. The hemoglobin concentration was 99%; the white blood cell count was 8,300. A serologic test of the blood gave a negative reaction. A chest roentgenogram showed no pathologic changes.

The patient has been afebrile and ambulant since his admission to the hospital.

He has been given 200 mg. of depo®-heparin (solution of heparin sodium in gelatin and dextrose) subcutaneously daily until the present (total 13 days). Before therapy was instituted the clotting time was 6 minutes. During treatment it has ranged from 10 to 13½ minutes.

After therapy was begun, the lesions of the axillae and groin began to dry rapidly and have flattened considerably. The eruption of the sternal area and back has responded more slowly. There are still erosions in this area with occasional new vesicles.

DISCUSSION ON PRECEDING TWO CASES

DR. R. B. STOUGHTON (by invitation): My colleagues and I have isolated a proteolytic enzyme from stool filtrates of patients with ulcerative colitis and have created in vitro "blister" formation with this enzyme. This "blister" formation occurs on human skin and has the histologic appearance of a pemphigus blister. A relatively normal basal layer remains; the spines of the rete cells become indistinct or totally absent. Such an enzymatic factor may be operative in pemphigus. A physiologic inhibitor of this enzyme is found in human serum albumin, and in albumin there appears to be some inhibitory effect on the enzyme by suramin, a polysulfonated compound.

For more than a month we have been observing the effects of heparin on one patient with pemphigus. The disease is kept under control with 300 mg. per day, but blisters re-form when the dosage is lowered.

We are now investigating the effects of other polysulfonated polysaccharides on this disease.

DR. HERMANN PINKUS, Monroe, Mich.: The inhibiting effect of heparin on the blood-clotting mechanism is well known. Suramin (naphuride®) sodium, also called germanin,® has a similar effect on that mechanism. I wonder if it may be more than coincidence that both these substances now have been used with some success in the treatment of pemphigus. Magner, Manson, and Pepple (A. M. A. ARCH. DERMAT. & SYPH. **64**:320 [Sept.] 1951) used heparin because it inhibits hyaluronidase. They mention that heparin is believed to originate in Ehrlich's mast cells. Recently, Asboe-Hansen called attention to the close parallelism between the number and activity of mast cells and the condition of the hyaluronic acid ground substance (*Acta dermat.-venereol.* **30**:221 and 338, 1950, and *Ann. Rheumat. Dis.* **9**:149, 1950). He believes that the mast cells secrete hyaluronic acid and that heparin may be an intermediary product in this process. If this is true, and if in pemphigus there is a defect in the normal mucopolysaccharide layer at the dermoepidermal junction, one could speculate that administration of heparin may act on this layer by a more direct mechanism than inhibition of hyaluronidase. Both of these angles seem to merit investigation.

DR. RICHARD WEISS, St. Louis: I know that you will all agree that it is premature to talk about the effects of heparin in the treatment of pemphigus. My associates and I have just secured some heparin for experimental purposes and have treated two patients. One had typical pemphigus fairly well controlled with oral administration of cortisone (cortone®). After about a month of treatment he was left with three or four ulcerations that did not heal. He was given 200 mg. of depo®-heparin daily for three days, and these ulcerations healed promptly. He was sent home and has done very well since with a maintenance dose of cortisone. Another patient with severe pemphigus was treated for months in the wards of Barnes Hospital, cortisone (cortone®) having been administered orally. His lesions also almost cleared with this therapy, but four or five superficial ulcerations did not heal. We attempted to use heparin, but a severe local reaction resulted. At each point of injection infiltration occurred under the skin with marked ecchymoses. He received only three injections, with little or no benefit.

The original report was on the treatment of only one patient, which, of course, does not mean very much, but I feel the benefit was sufficient to warrant our trying the drug in other patients. This being done in many dermatological centers will give us an accumulation of information in a few months, and perhaps at the meeting of the American Medical Association a preliminary evaluation of depo®-heparin may be attained.

DR. THEODORE CORNBLEET: Last year I presented a man with the acquired form of urticaria pigmentosa on whom my colleagues and I made observations with the local use of toluidine blue and heparin. With appropriate stains we thought we saw changes in the mucopolysaccharides.

In the present patient with familial pemphigus, itching subsided and the lesions involuted promptly with aureomycin therapy. The antibiotic gave her "stomach distress," and the lesions returned when use of the drug was discontinued. She tolerated a smaller dose better, with clearance again of the eruption. If this disease is determined by inheritance, why should an action against bacteria help? Just now it is being found that the changing of the intestinal flora with antibiotic administration influences the liver. The porphyrins, sometimes associated with some bullous diseases, may originate in a diseased liver too.

**Case for Diagnosis: Periarteritis Nodosa?** Presented by Dr. James H. Mitchell.

**Erythema Multiforme with a Histologic Picture of Periarteritis Nodosa.** Presented by Dr. Herbert Rattner, Dr. Harold Rodin, and (by invitation) Dr. J. F. Sickley.

The patient is a 45-year-old white man. He states that he has had a "skin rash" for the past 10 years. The eruption begins as "hives" which vary in size from a few millimeters to large plaques. Some of the lesions itch. The rash may appear on any part of the body, but within 24 hours the entire cutaneous surface is involved. The rash usually lasts about three days and then spontaneously subsides. With the appearance of the eruption, there are accompanying swelling and pain in the joints (hands, wrists, ankles, and knees). The patient believes that the severity of the eruption depends upon the amount of exertion. While he was hospitalized in 1948, the eruption appeared at weekly intervals but was mild.

Eight months ago several ulcerations developed on the left leg which have failed to heal.

He states that for the last 18 years he has taken either a "Carter's Little Liver Pill" (a preparation of podophyllum resin and powdered purified aloes) or "N. R." laxative (a preparation of aloes, frangula, apocynum, burdock, dandelion, sarsaparilla, mandrake, rhubarb, prickly ash bark, and juniper berries) every night.

Physical examination shows a generalized urticarial and purpuric eruption which is most marked on the extremities and shoulders. The lesions are sharply defined, raised, erythematous, and of varying shapes and sizes. On the left leg there are many small ulcerations which have granulomatous bases and are covered with a dry serosanguineous exudate. On laboratory studies urinalysis gave normal results. The hemoglobin concentration was 87%; the white blood cell count was 7,300, with 50 polymorphonuclear leucocytes, 35 lymphocytes, 3 band forms, 9 monocytes, and 3 eosinophiles, per 100 cells. Serologic reactions of both blood and spinal fluid were negative. The electrocardiogram was normal. A chest roentgenogram and a gastrointestinal series showed no pathologic changes. Blood chemical studies disclosed 7 gm. of total protein, 41 mg. of nonprotein nitrogen, and 1.94 gm. of gamma globulin per 100 cc. The cephalin-flocculation reaction was 2+, and thymol turbidity was 2.6 units. A skin biopsy revealed the picture of periarteritis nodosa.

DISCUSSION ON TWO PRECEDING CASES

Dr. Frederick R. Schmidt: The type of eruption seen in the second patient is not uncommon in countries where trichinosis is prevalent. In the Latin-American countries I saw several persons who had this hemorrhagic type of eruption with necrotic lesions. After seeing a few of these cases which had been diagnosed as toxic erythema, I examined histologically specimens of skin taken from these patients, and to my surprise they showed the picture of periarteritis nodosa. Two of these slides I submitted to Dr. Louis Winer, who made a diagnosis of periarteritis nodosa. I published a report on this about a year ago (Chaná, P., and Schmidt, F. R.: Periarteritis Nodosa with Cutaneous Lesions, *Urol. & Cutan. Rev.* **54**:408-409, 1950). We must not forget that there is a so-called benign form of periarteritis nodosa which may persist for many years and is possibly identical with nodular vasculitis. The vascular lesions may be produced not only by the trichinellae but by large doses of corticosteroids. I believe that this is an eruption of the toxic type and that we may have to enlarge our conception of periarteritis nodosa to include (*a*) cases of the idiopathic, fatal form and (*b*) those of the benign type, secondary to many different agents. Both of these patients present one of the cardinal symptoms of periarteritis nodosa, i. e., severe abdominal pain. I believe that the second man showed a histologic picture of periarteritis nodosa.

DR. M. H. KULWIN, Champaign: Several years ago an article appeared concerning a large series of cases of nonthrombocytopenic purpura of the Henoch and Schönlein group. Biopsies were performed, and many showed a histologic picture of periarteritis nodosa.

DR. A. C. CURTIS, Ann Arbor, Mich.: From what Dr. Schmidt said and from Dr. Louis Winer's work, I think we should broaden our concept of periarteritis nodosa. Many lesions which result from allergic manifestations are associated with a tremendous amount of vascular change. These vascular changes occur in localized eruptions, such as erythema nodosum or erythema multiforme. Similar changes may be generalized in periarteritis nodosa. The vascular insult in each instance is a result of an allergic state. If the eruption produced is a localized one, such as erythema multiforme, it may disappear with complete repair and no residual defects. If it is a generalized disease, such as periarteritis nodosa, it may lead to death or the patient may recover with permanent damage to large areas of the vascular bed. I think we have all seen patients with periarteritis nodosa who have lived through the acute manifestations of the disease, whose disease remains inactive but permanently impairs the function of some vital structures.

DR. H. E. MICHELSON, Minneapolis: Those of us who have services closely associated with departments of internal medicine are frequently called upon to make a diagnosis of a skin lesion when the clinician thinks the patient has periarteritis nodosa. I have found this most difficult, and I have seen lesions from the most insignificant erythema up to a hemorrhagic lesion with necrosis occur in that disease; therefore, I believe there is no specific cutaneous lesion. As far as the microscopic examination of the skin lesion is concerned, in the few cases observed I have not seen good results with any of the so-called newer drugs. I have seen patients with spontaneous improvement when the outlook was very dark, with recurrences later.

DR. HAROLD RODIN: This patient has been under observation for 10 years with a diagnosis of erythema multiforme perstans. A complete physical and laboratory examination on several occasions has failed to reveal any organic disturbance to account for his cutaneous symptoms.

We are grateful to Dr. Schmidt for his suggestion that a trichinosis may be the underlying factor in this case. A biopsy will be performed on one of his muscles and a search made for the parasite.

**Calcinosis Cutis.** Presented by DR. FREDERICK J. SZYMANSKI.

A. J., a 49-year-old white woman, was first seen in the Dermatology Clinic, University of Illinois Research and Educational Hospitals, on Aug. 23, 1951. Five years ago the patient had pain and swelling in both wrists, elbows, and knees, and the fingers and neck. A diagnosis of rheumatoid arthritis was made. She then had difficulty with swallowing and was hospitalized at Michael Reese Hospital, where a muscle biopsy specimen was diagnosed as showing dermatomyositis.

About three years ago the patient began to display many nodules and tumors over the body and extremities. Occasionally, one of these nodules would become fluctuant, break down, and give off a milky fluid and chalky particles. As soon as all this chalky material was extruded from the wound, healing would take place, leaving a deep scar.

A piece of tissue was removed from a nodule on the left forearm. The histologic sections revealed hyperplasia of the epidermis and fibrosis of the corium with a few flecks of calcification.

Laboratory examinations revealed that the results on concentration and dilution tests were all within normal limits. The hemoglobin concentration was 12.8 gm. per 100 cc.; red blood cells numbered 4,500,000, and white blood cells, 6,700, with 52% neutrophiles, 1% monocytes, 42% lymphocytes, and 5% eosinophiles. The Wassermann and Kahn reactions were negative. The fasting blood sugar level was 81 mg., nonprotein nitrogen, 32 mg. (normal, 25 to 35 mg.), and uric acid, 2.5 mg. (normal, 1 to 3 mg.), per 100 cc. Serum albumin was 4.4 gm. (normal, 4.6 to 6.7 gm.); serum globulin, 4.5 gm. (normal, 1.2 to 2.3 gm.), and total serum protein, 8.9 gm., per 100 cc. Inorganic phosphorus was 4.1 mg. (normal, 3 to 4 mg.), alkaline phosphatase, 4.2 units (normal, 2 to 4 units), and calcium, 7.6 mg. (normal, 9 to 11 mg.), per 100 cc. of serum.

A roentgenogram showed the esophagus to be normal. Marked subcutaneous calcifications were noted on the chest film, overlying the lung fields and in the soft tissues of the axillae and lateral chest walls bilaterally.

Roentgenograms of the hands showed periarticular demineralization. However, no evidence of rheumatoid bone changes was present. Marked soft tissue calcifications were noted in both wrist regions.

**Acrosclerosis.** Presented by DR. ALFRED B. FALK and (by invitation) DR. FRANCIS HETREED.

**Linear Scleroderma.** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

DISCUSSION ON PRECEDING THREE CASES

DR. A. C. CURTIS, Ann Arbor, Mich.: The first case was an excellent example of the concept recently developed by Dr. Clayton Wheeler that calcinosis is not in itself a primary disease. The primary cause of localized calcinosis may be infection, a foreign-body reaction to such things as injections of irritating substances, or a trauma, as in tennis elbow or bursitis. It may be very generalized, as in trichinosis, or due to the collagenous tissue diseases, such as scleroderma or dermatomyositis. The pathologic section of the muscle removed several years before this patient displayed calcinosis is an excellent example of active dermatomyositis. This patient then illustrates a disseminated collagenous tissue disease (dermatomyositis) which was followed by a secondary deposition of calcium in the diseased areas.

DR. THEODORE CORNBLEET: A woman at the Cook County Hospital with scleroderma of fingers and hands has relief with almost normal flexion possible as a result of local injections of hyaluronidase. Unfortunately her respiration is embarrassed by pulmonary changes, and I don't know how to get hyaluronidase to act on these.

The woman with calcinosis has a low blood calcium level, yet this did not deter these formations. But she did have a high serum protein level of 8.9 gm. I have seen this before in calcinosis. Perhaps there is a disturbance of protein patterning here to explain the unusual calcium binding. Hormonal relationships could be studied in this case. Clegg and others (*Science* **114**:437, 1951) showed that injection of diethylstilbestrol in birds will cause changes associated with egg formation to occur in the serum proteins, together with changes in the total serum calcium and phosphorus; the increased serum proteins bind increased amounts of calcium.

DR. F. J. SZYMANSKI: There are many classifications of calcinosis cutis in use today, but the simplest divides this condition into two forms: 1. The metastatic variety is associated with hypercalcemia and is seen in such conditions as parathyroid tumors, chronic nephritis, and hypervitaminosis D. 2. The metabolic type is associated with normal serum calcium levels and occurs secondarily to dermatomyositis, scleroderma, basal-cell tumors, and other lesions too numerous to mention. I feel that our case belongs to the latter group, inasmuch as the sections taken from the thigh muscle were diagnostic of dermatomyositis.

**Dystrophic Epidermolysis Bullosa with Alopecia.** Presented by DR. CALVIN J. DILLAHA (by invitation).

At the age of 2 months B. C., a 2½-year-old girl, first had skin lesions characterized by a vesicular erythematous crusted dermatitis involving areas of pressure or friction. This was accompanied with complete alopecia at 5 months of age. The skin eruption has persisted to date, along with the alopecia and nail changes, except for a period of approximately three months at one year of age, at which time the child was completely free of any cutaneous disorder.

The patient's general health and development have otherwise been normal.

There is no family history of similar cutaneous disease.

Physical examination showed a child of normal development and growth. The eruption involved the skin of all areas of pressure or friction, i. e., the forehead, cheeks, perioral area, the elbows, both hands, the sides of the fingers, the paronychial areas, the heels, ankles, and the inner aspect of the thighs, the knees, buttocks, and perianal region. The lesions consisted of

crusted superficial erosions surrounded by epithelial fringes. A few bullae were present on the feet. All the nails except one showed dystrophic changes. The scalp was covered with a growth of lanugo hair. The teeth were normal.

Therapy has consisted of application of bacitracin ointment and a zinc oxide paste with protective dressings. With this management healing of the lesions has been satisfactory. However, many lesions now show induration suggesting early hypertrophic scar formation.

Results of routine laboratory tests were normal. The reaction to the Kahn test was negative. A 24-hour urine specimen contained 89 γ of coproporphyrin and no uroporphyrin.

A biopsy specimen shows a large intraepidermal vesicle secondarily infected. On each side of this, there are multiple small intraepidermal vesicles. On one end of this section there is prominent acanthosis with prolonged rete pegs. Throughout the upper corium there is an extensive infiltrate consisting of lymphocytes, histiocytes, fibroblasts, and many polymorphous forms.

DISCUSSION

DR. S. W. BECKER: This child presents a very interesting picture. My impression as I looked at it was that it did not quite correspond to the ordinary picture of epidermolysis bullosa. The lesions about the mouth suggest rather a systemic moniliasis. I did not notice any report in the history on whether examination for fungi had been made. The alopecia is extremely interesting. If the child had systemic moniliasis, the alopecia might be on a symptomatic basis. However, usually following such alopecia there is a recurrence of the normal growth of hair. This child's hair is all of the lanugo type.

DR. HERMANN PINKUS, Monroe, Mich.: I agree with Dr. Becker that other diagnoses should be considered in this case. I did not see any of the scars or contractures which occur so regularly at an early age in dystrophic epidermolysis bullosa. The microscopic picture was that of an acute dermatitis with intraepidermal vesiculation. The loss of hair certainly is a striking feature and reminded me of the group of cases which Dr. N. Danbolt, of Oslo, Norway, spoke of when he visited this country some years ago. He described as acrodermatitis enteropathica (Danbolt, N., and Closs, K.: *Acta dermat.-venereol.* **23**:127, 1942) an often familial condition which has some resemblance to generalized moniliasis and is always associated with loss of hair. This child apparently does not have the attacks of diarrhea and steatorrhea which the Scandinavian authors describe, but she certainly has the "family resemblance" that is evident in the published pictures of Danbolt's patients.

DR. CALVIN DILLAHA (by invitation): Direct examination of skin scrapings from this patient showed no fungi. Cultures have been taken, but to date results have not been reported. We appreciate very much the suggestion of Dr. Pinkus that this patient may have the condition described by Dr. Danbolt.

ADDENDUM.—Numerous cultures from lesions of this patient did grow a yeast, and by rabbit inoculation and differential culture the organism was found to be Candida albicans. However, after therapy with Castellani's paint (a preparation of basic fuchsin, phenol, boric acid, acetone, and resorcinol), the cultures became sterile. After this therapy and while the patient was being observed in the hospital, superficial bullae have continued to develop on areas of pressure without an initial inflammatory response. Danbolt and Closs (*Acta dermat.-venereol.* **23**:127, 1942) describe two children with a very similar clinical picture, including the alopecia, but also with gastrointestinal and metabolic disturbances. In our patient results of repeated dextrose-tolerance tests and studies of gastrointestinal function were considered to be within normal limits.

**Urticaria Pigmentosa Treated with Toluidine Blue.** Presented by DR. ALLAN L. LORINCZ (by invitation).

Mr. M. G., a 43-year-old textile salesman, came to the University of Chicago Clinics in August, 1951, complaining of a pruritic skin eruption present since the age of 10 years. This eruption gradually appeared in the form of discrete dark purplish-brown macules over the legs which became pruritic and urticarial after scratching. The eruption slowly and progressively became more extensive. By the age of 30 years it was generalized and had become confluent over many areas. Besides local urtication of the lesions, there have been general urticarial dermographism and also distinct urticarial outbreaks following the ingestion of certain

foods. There has been no other disturbance of health except for an episode of migratory arthritis one year ago of unknown origin which ceased after corticotropin and cortisone therapy given elsewhere. This hormone therapy had no effect whatever on the skin eruption. There is no family history of similar skin disorders.

Therapeutic attempts elsewhere with various local applications and x-ray irradiation were of no benefit. Administration of antihistaminic agents in large doses did control pruritus and urtication to a moderate extent.

Results of physical examination were noncontributory except for the skin eruption. Routine urinalysis, blood counts, and chest roentgenogram all showed an essentially normal condition. The Kahn reaction was negative. A protamine-titration test failed to reveal any increase of heparin-like substances in the blood, and no disturbance in the blood-coagulation mechanism could be found.

Four weeks ago toluidine blue therapy was initiated with the intravenous administration of 1.2 gm. of the dye over a three-day period. Treatment was then continued with the oral administration of 300 mg. of toluidine blue daily. A total of about 10 gm. of the dye has been given so far. Within 48 hours after toluidine blue therapy was started, the patient reported considerable relief from itching. This relief has been maintained as long as oral therapy has continued. Urtication of the lesions, though still present, has also been reduced in degree during this period.

Discontinuance of use of the drug for 36 hours was followed by a severe recurrence of urticaria and pruritus, according to the patient. The color of the skin lesions has not changed.

DISCUSSION

DR. THEODORE CORNBLEET: Toluidine blue is an antagonist of heparin. Since the granules in the mast cells, so plentiful in urticaria pigmentosa, supposedly contain heparin, it is rational to use that dye. The man with urticaria pigmentosa I mentioned in an earlier discussion received little help from toluidine blue treatment.

DR. ALLAN L. LORINCZ (by invitation): Toluidine blue is a dye closely related to methylene blue. It has the property of combining with acid polysaccharides, such as occur in heparin, so as to stain them metachromatically. Because the granules of mast cells show intense metachromasia with this dye and have been demonstrated to be closely related to heparin, we felt that the chemical alteration of these granules by the dye in the characteristic cells of urticaria pigmentosa lesions might also change the associated urtication. With the massive doses of toluidine blue used here, there have been relief of itching and suggestive reduction of urtication, but otherwise not much change has occurred in the appearance of the lesions. We do not yet generally recommend this massive toluidine blue therapy because clinical use of this dye is still experimental. Dr. J. G. Allen, of our surgical department, has pioneered the use of toluidine blue as an antiheparin agent. Its use in this patient has been under his supervision.

DR. MICHAEL H. EBERT: Did you do biopsies after you used toluidine blue to see if there were any changes?

DR. ALLAN L. LORINCZ (by invitation): We did perform biopsies both before and after treatment. Unfortunately mast cells could not be well demonstrated on either occasion; therefore, I cannot report on changes in them.

ADDENDUM.—A biopsy specimen taken from this man several years ago by another physician was reported to show massive mast-cell infiltrates.

**Amebiasis with Leg Ulcers.** Presented by DR. MICHAEL H. EBERT, DR. ALLEN PEARL, and (by invitation) DR. J. F. SICKLEY.

DISCUSSION

DR. RICHARD S. WEISS, St. Louis: I have been told that about 10% of the population of the United States are ameba carriers; therefore, the finding of amebae in the stool does not necessarily mean that amebae are in the skin. Moreover, the ulcers on the skin do not look like the amebic ulcers described by M. F. Engman Sr., and later by M. F. Engman Jr. and Meleney. The ulcers of amebiasis affecting the lower extremities are superficial, but they

have very definite undermined borders. The ulcers are usually surrounded by a brilliant red halo. The diagnosis is difficult to make unless one demonstrates the amebae.

Amebiasis of the abdominal wall following operations shows a similar but much more massive picture. Amebae can usually be fairly easily demonstrated by scraping the undermined border and examining the scrapings microscopically on a warm stage. Amebae in the lesions on the extremities are much harder to demonstrate. They can be shown in sections from the lesions.

DR. MICHAEL H. EBERT: The title for this presentation was used purposely. It has been proved without any doubt that the patient has an amebic infection of the bowel with ulcer formation. Up to the present, however, we have not been able to demonstrate the amebae in the ulcers. I was particularly pleased to hear Dr. Weiss say that at times the amebae were very difficult to demonstrate in these ulcers. At various times the ulcers on the leg have had a very different aspect from their present one. At one time they suggested a bromide eruption. The blood bromides were found to be normal. Careful examinations were made in the mycology laboratory at the Cook County Hospital for deep mycotic infections, as well as for Candida, with negative results. It is only within the past week that amebiasis of the colon has been demonstrated. Her history states she was operated on for what was supposed to be empyema of the gall bladder. This may well have been an amebic abscess. After the operation she did not recover her weight or strength. The ulcers developed which are under discussion today.

NOTE.—Since the meeting, the patient has been treated for amebiasis. The ulcers were practically healed within two weeks. The patient's general condition is much improved.

**Kaposi's Hemorrhagic Sarcoma Associated with Lymphoblastoma, Type Undetermined.** Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI.

DISCUSSION

DR. STEFAN BIELINSKI (by invitation): This man had been hospitalized at Cook County Hospital on several previous occasions. On biopsy a diagnosis of lymphoblastoma was made. He was treated at the Anemia Clinic. He had enlarged lymph glands in the mediastinum and in the cervical area and axillae and some dysphagia. These all melted down after 14 x-ray treatments. He got along fairly well until three months ago, when the bluish nodules started to develop on the right thigh. They gradually progressed until they covered the upper two-thirds of the right thigh. He was admitted for a biopsy of one of the nodules, and the diagnosis was Kaposi's hemorrhagic sarcoma. Another biopsy specimen of a lymph node taken during this hospitalization was reported as showing lymphoblastoma, type undetermined.

DR. M. R. CARO: I think that this is a rather important case in that it links Kaposi's sarcoma with the lymphoma group. On a number of occasions I have seen cases of Kaposi's sarcoma with a blood picture of pseudoleukemia and a leucocyte count of 40,000 or 50,000. This is the first case I have seen, however, in which the biopsy specimen of the cutaneous lesions showed Kaposi's sarcoma and that of the lymph nodes showed unmistakable lymphoma.

DR. FREDERICK J. SYZMANSKI: The association of lymphoblastoma and Kaposi's sarcoma has been noted on five different occasions in the world's literature. This fact is a point in favor of the reticuloendothelial origin of Kaposi's sarcoma.

DR. THEODORE CORNBLEET: Dr. Michelson saw this man with me. He remarked that Max Joseph used to say that when the hands and feet were clear there was no multiple hemorrhagic sarcoma present. This particular patient, whose hands and feet are unaffected, proves the falsity of that dictum.

**Prurigo Nodularis.** Presented by DR. JAMES R. WEBSTER and (by invitation) DR. OLIVER RIAN.

**Pityriasis Rubra Pilaris.** Presented by DR. ALFRED B. FALK and (by invitation) DR. FRANCIS HETREED.

**Case for Diagnosis: Dermatitis Herpetiformis? Habermann's Disease (Pityriasis Lichenoides et Varioliformis Acuta)?** Presented by DR. ALLAN L. LORINCZ (by invitation).

**Herpes Zoster: Postherpetic Motor Paralysis.** Presented by DR. MATTHEW J. BRUNNER.

**Case for Diagnosis: Dermatitis Factitia?** Presented by DR. CLARK W. FINNERUD and DR. FREDERICK J. SZYMANSKI.

**Acrodermatitis Continua(?).** Presented by DR. FRANCIS E. SENEAR, DR. J. B. HAEBERLIN JR., and (by invitation) DR. RAYMOND R. SIMPSON.

**Huge Verruca Plantaris(?).** Presented by DR. A. W. STILLIANS.

**Case for Diagnosis: Sarcoid?** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. STEFAN BIELINSKI.

**Granuloma Inguinale.** Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Stefan Bielinski.

**Keratoderma Blennorrhagica(?).** Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. J. F. Sickley.

**Lymphoblastoma, Type Undetermined; Generalized Papular Eruption.** Presented by Dr. Michael H. Ebert, Dr. Vera Leaf, and (by invitation) Dr. Stefan Bielinski.

**Senile Elastosis with Senile Sebaceous Adenoma.** Presented by Dr. Theodore Cornbleet, Dr. David M. Cohen, and (by invitation) Dr. J. F. Sickley.

**Tuberculosis Cutis; Tuberculosis Verrucosa Cutis(?).** Presented by Dr. Theodore Cornbleet, Dr. David M. Cohen, and (by invitation) Dr. Stefan Bielinski.

**Actinomycosis(?); Tuberculosis(?).** Presented by Dr. Herbert Ratiner, Dr. Harold Rodin, and (by invitation) Dr. Stefan Bielinski.

**Discoid Lupus Erythematosus.** Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Stefan Bielinski.

**Kaposi's Varicelliform Eruption.** Presented by Dr. David Omens.

**Stephen Rothman, M.D., *President***

**James R. Webster, M.D., *Secretary***

***Nov. 21, 1951***

**Bullous Disease, Herpes Gestationis(?).** Presented by Dr. Theodore Cornbleet, Dr. Henry Schorr, and (by invitation) Dr. J. F. Sickley.

DISCUSSION

Dr. Oliver S. Ormsby: Several years ago I had a patient with herpes gestationis. She was very ill. I gave her some serum from another patient in the hospital in the same stage of gestation with excellent result. She began to get better right away, and within a little while the eruption was practically cleared. I have not seen any reports on this treatment, but it would be well worth while for one to remember it if a case of this sort is encountered.

Dr. Stephen Rothman: Is it normal human serum or pregnant serum?

Dr. Oliver S. Ormsby: It was just serum from another pregnant woman in the same stage of gestation.

Dr. Frederick R. Schmidt: Some years ago an Australian physician brought to our notice the fact that women with rubella during pregnancy gave birth to a high incidence of children with congenital defects. About two years ago it was reported that women with herpes gestationis also gave birth to a large number of defective offspring.

Dr. S. J. Zakon: About eight years ago I had under my care a patient with herpes gestationis who carried to term. The child was normal. The lesions disappeared after the uterus was emptied. In the recent literature there are reports on the use of progesterone in rather large doses in herpes gestationis with good results. Perhaps the treatment of Dr. Ormsby, utilizing serum from a normally pregnant woman, is based on the same principle.

Dr. M. R. Caro: A longer period of observation will be necessary before we can be sure that this condition is herpes gestationis. Some features suggest to me that it may be pemphigus vulgaris. Histologically, the section showed vesicles in the epidermis with no eosinophilic cells in the vesicles, and that is very unusual for herpes gestationis. Before we empty the uterus or consider other drastic treatment, we should observe her longer.

Dr. Stephen Rothman: Has sulfapyridine any effect in herpes gestationis? This would indicate that the two diseases, dermatitis herpetiformis and herpes gestationis, have an identical cause.

Dr. H. H. Rodin: In a patient with herpes gestationis that I treated a year ago, sulfapyridine therapy failed completely. The patient also failed to respond to aureomycin therapy. Because of her serious illness, it was found necessary to induce labor in the eighth month.

Although improvement occurred after termination of pregnancy, the bullous lesions continued to develop. Again sulfapyridine was tried without success. Then, as is usual in conditions which fail to respond to the newer drugs, an old remedy was tried. Potassium arsenite (Fowler's) solution was administered, with prompt relief of her symptoms. Whether recovery was due to the arsenic or was incidental to the therapy, I do not know, but she recovered within one week.

Furthermore, she continues to have recurrent attacks of herpetic lesions without pregnancy, which suggests that herpes gestationis is a variant of dermatitis herpetiformis.

DR. THEODORE CORNBLEET: The utility of pregnancy serum in herpes gestationis suggests the possibility of cortisone's usefulness as a parallel to the effectiveness of pregnancy serum in rheumatoid arthritis.

Since herpes gestationis occurs in relation to pregnancy and sometimes repeatedly during successive pregnancies, it seems that any injury to the fetus occurring with any regularity because of this disease would appear in the literature. The eruption in this woman looks much more to me like dermatitis herpetiformis than like pemphigus. The lesions are grouped; they are practically all vesicles; there is no odor; the woman remains in good health despite her widespread eruption, and the eruption came on during pregnancy. We shall try sulfapyridine and let Dr. Rothman know if it is effective here.

**Partial Gangrene of the Toes Due to "Mycotic" Embolism and Aneurysm of the Posterior Tibial Artery.** Presented by DR. JAMES R. WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI.

DISCUSSION

DR. STEPHEN ROTHMAN: Nondermatologists speak quite frequently about "mycotic embolism." We dermatologists do not know what they mean. I should like to ask the presenters to outline the history and significance of this debatable concept.

DR. SAMUEL BLUEFARB: When we saw this woman a month ago, she had a gangrenous process on the foot due to an embolus following subacute bacterial endocarditis. The surgeon believed that removal of the embolus with the aneurysm would possibly divert the gangrenous process. Ten days ago this operation was done with the result that the circulation has returned to the toes and the skin color is much lighter than it was a month ago.

**Alopecia Universalis Treated with Cortisone Acetate Given Orally.** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. CALVIN J. DILLAHA.

G. R., a 34-year-old machinist, began losing hair from his eyebrows and beard at the age of 24 years. Within a short period the scalp and body were involved also with a diffuse nonpatchy loss of hair and in six months from the initial onset this process had evolved into alopecia universalis. At this same time his fingernails began to break off easily and frequently fissured longitudinally. The latter condition corrected itself in a few months, but there has never been any significant regrowth of hair.

After four weeks of oral cortisone acetate therapy (150 mg. daily), new hair was noted over the entire body except the axillary and pubic regions. Growth of the eyelashes and eyebrows has been scant. After several weeks the dosage was reduced to 100 mg. daily.

At present (two months after initiation of therapy) the hair has continued to grow, and the scalp hair is approximately ½ in. (1.3 cm.) in length, pigmented, firmly rooted, and of normal texture.

Pictures of the scalp before and during therapy are presented.

This patient is one of a group of eight patients with varying degrees of alopecia areata treated with cortisone of whom six have shown regrowth. In each patient regrowth was detectable four weeks after initiation of therapy.

**Alopecia Areata Fere Universalis Treated with Cortisone Acetate, Given Orally.** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. CALVIN J. DILLAHA.

S. O., a 35-year-old laborer, displayed alopecia universalis within eight months after a patchy baldness appeared on the scalp at the age of 26 years.

The only regrowth during the past nine years has been a few terminal hairs scattered over the scalp.

After four weeks' administration of cortisone orally (150 mg. daily), new hair was growing in all areas except the axillary and pubic regions. After five weeks the dosage was reduced to 100 mg. daily, and it was again lowered in 12 days to 75 mg. daily.

After eight weeks of therapy, the scalp hair, beard, eyebrows, eyelashes, and body hair have continued to grow, although the growth is not entirely uniform. The hair is well pigmented, firmly rooted, and approximately ½ in. (1.3 cm.) in length.

Photographs of the scalp before and during therapy are presented.

This patient is one of a group of eight patients having varying degrees of alopecia areata treated with cortisone acetate orally, of whom six have shown regrowth. Regrowth was detectable in each patient four weeks after initiation of therapy.

### DISCUSSION ON PRECEDING TWO CASES

DR. S. J. ZAKON: There was a press release to the effect that cortisone has hair-growing properties, and a patient with alopecia areata came to me with a request for cortisone therapy. I asked him to wait until more confirmatory reports appeared. However, he obtained and took 100 cortisone tablets without any noticeable improvement. Dr. Rothman's patients do show a growth of hair, and I should like to ask Dr. Rothman what will happen to this hair growth when the cortisone therapy is withdrawn?

DR. CALVIN J. DILLAHA (by invitation): Referring to Dr. Zakon's remarks, we observed that hair growth was detectable after only one month's therapy with at least 100 to 150 mg. of cortisone given orally daily.

The two patients presented today are part of a group of eight patients with alopecia areata that we have treated, of whom six have shown a regrowth of hair. The alopecia in all these patients was of at least five years' duration. One has been receiving therapy since June and now has new hair 2½ in. (6.4 cm.) long. It is interesting to note that in the two patients in whom regrowth did not occur the alopecia had its onset prior to puberty and was present during puberty.

Treatment has not been stopped as yet in any patient showing regrowth. In one patient the regrowth has continued with a maintenance dose of 25 mg. of cortisone daily. Side-effects from this type of therapy have so far offered no difficulty.

DR. JULIUS E. GINSBERG: I thought it was quite remarkable that these patients had alopecia for six or seven years and yet with treatment were able to grow hair of a mature nature.

DR. STEPHEN ROTHMAN: I do not believe that this effect has anything to do with effects of cortisone on physiological hair growth. Cortisone, on the one hand, may cause hirsutism in man; on the other hand, on local application it inhibits hair growth in animals. Here we have to deal with an effect on the unknown causative agent of alopecia areata. In an earlier study, Dr. S. A. Walker and myself (*J. Invest. Dermat.* **14**:403-413, 1950) found the following endocrine influences: 1. The course is much severer when alopecia areata begins before puberty. 2. Some patients with alopecia totalis recover completely during pregnancy and lactation. 3. In some patients the onset is simultaneous with that of thyrotoxicosis. On the basis of the two first observations we could predict that cortisone therapy will be effective by altering the soil upon which the unknown causative agent of alopecia areata acts. I cannot understand the comment that this is fuzz. This is fully developed well-rooted normally pigmented terminal hair. One patient is compelled to shave his beard again after a rest period of several years.

DR. S. J. ZAKON: At the last meeting of the American Medical Association in the Session on Allergy, it was stated that in the near future we are going to have cortisone addicts as well as addicts to morphine. The state of euphoria, the feeling of well-being, and the desire to continue cortisone administration even long after the physician discontinues it are real dangers that we should properly consider. I believe there will always be druggists who will continue to sell this drug over the counter for a price. This element also must be considered.

DR. STEPHEN ROTHMAN: Of course, I heartily agree with Dr. Zakon in his concern about whether such therapy will be practicable or not. This will primarily depend on the required maintenance dose, which is not yet established. One patient has shown active growth with 25 mg. of cortisone daily, but we don't know whether this will go on or whether other patients will behave similarly. The patients were presented in order to demonstrate a most remarkable experimental finding and not in order to recommend the method for therapy. It is too early for that.

DR. THEODORE CORNBLEET: Does cortisone act as a protective agent against some cause?

DR. STEPHEN ROTHMAN: I would think so. The unknown cause seems to ravage more uninhibitedly on the scalp in cases with prepubertal onset than in cases with postpubertal onset. Therefore, and because of frequent recovery during pregnancy, it is reasonable to assume that cortisone counteracts the unknown cause.

**Case for Diagnosis (Boy with Yellowish Areas over Buttocks).** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. ALLAN L. LORINCZ.

Four years ago the parents of J. F., an 11-year-old boy, noted the appearance of firm yellowish areas over his buttocks. These have gradually enlarged and become more numerous since then. Additional similar lesions have appeared on the right shoulder, right upper arm, and several areas of the trunk. There have been no subjective complaints.

The lesions consist of intracutaneous, firm, pale yellow, indurated plaques, some of which extend into the subcutaneous tissue. Physical examination, except for the skin lesions, revealed an essentially normal condition. There is no family history of similar disease. The boy is overactive and slightly obese. There is a history suggestive of polydipsia and polyuria.

Routine urinalysis and blood counts gave normal results except for eosinophilia (6%). Roentgen examinations of the chest, skull, and pelvis revealed no bony abnormalities or soft-tissue calcification.

A lesion over the right upper arm was excised for biopsy. Histologic sections revealed focal areas of mild collagen degeneration without any cellular infiltration. These focal areas of collagen alteration are well defined by the Van Gieson stain and focal clumping of the elastic fibers. Some of the blood vessels show thickening of their walls and even obliteration of the lumen.

Fat stains with Sudan IV and Sudan black were negative for lipids.

DISCUSSION

DR. HAROLD SHELLOW: I examined this patient before I read the history. Clinically there was some suggestion of the edematous stage of a colloid degeneration of the skin. When I read the history and found there was such a change, I was more encouraged by the possibility of this disorder. I cannot help but interject also the possibility of pseudoxanthoma elasticum. Perhaps examination of the retina will show some angioid streaks to confirm this diagnostic possibility.

DR. GEORGE C. WELLS (by invitation): In considering this case with the lumps over the back, I thought of a rare condition called connective-tissue nevus. This has grouped yellowish lesions, resembling little patches of morphea; or there may be aggregates of smooth papular lesions that suggest the synonym "cobblestone nevus." It is remarkable how little you see in histological sections. You look in vain for obvious changes in collagen or elastica.

DR. M. R. CARO: It was my impression that these lesions were nodules and were entirely subcutaneous. The lesions were identical clinically with those seen in subcutaneous fat necrosis in the newborn and in fat persons. I wonder if a biopsy specimen of one of these nodules taken very deeply would not show some necrotic tissue in the fat tissue.

**Paget's Disease of the Breast Near the Nipple.** Presented by DR. DAVID COHEN, DR. THEODORE CORNBLEET, and (by invitation) DR. STEFAN BIELINSKI.

**Ulcers on the Legs in a Patient with Amebiasis.** Presented by DR. MICHAEL EBERT and (by invitation) DR. ALLEN PEARL, Oak Park, and DR. J. F. SICKLEY.

**Ehlers-Danlos Syndrome.** Presented by DR. MICHAEL EBERT and (by invitation) DR. ALLEN PEARL, Oak Park, and DR. J. F. SICKLEY.

**Xanthomatosis.** Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

**Gout.** Presented by DR. JAMES R. WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

**Erythrodermic Psoriasis, Relapse After Corticotropin Therapy.** Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

**Mycosis Fungoides in a Negro.** Presented by DR. MICHAEL EBERT, DR. VERA LEAF, and (by invitation) DR. STEFAN BIELINSKI.

**Neurofibromyxosarcoma.** Presented by DR. JAMES R. WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

**Case for Therapeutic Suggestions: Purpura Annularis Telangiectodes (Majocchi)?** Presented by DR. MICHAEL H. EBERT and (by invitation) DR. HAROLD M. SPINKA.

**Bromoderma.** Presented by DR. ROYAL IHRKE and (by invitation) DR. B. J. PASS.

**Granuloma Annulare (?).** Presented by DR. JAMES H. MITCHELL and (by invitation) DR. ROBERT M. GOODWIN, Springfield.

**Nevus on Hand and Foot.** Presented by Dr. Theodore Cornbleet.

**Acrodermatitis Chronica Atrophicans with Pseudoscleroderma, Ulcers, and Nodules.** Presented by Dr. A. Goldberg and (by invitation) Dr. B. J. Pass.

**Cylindroma.** Presented by Dr. E. M. Smith and Dr. R. M. Oliver.

**Bullous Lichen Sclerosus et Atrophicus vs. Vesicular Lichen Planus.** Presented by Dr. F. E. Senear and staff.

**Papular Keratoses of the Extremities.** Presented by Dr. Francis E. Senear and Dr. Irene Neuhauser.

**Leprosy (Hansen's Disease), Remission with Sulfoxone Sodium (Diasone®) Therapy.** Presented by Dr. Paul K. Weichselbaum.

**Nevus Unius Lateralis.** Presented by Dr. David Cohen and Dr. S. J. Zakon.

**Scleroderma with Bullae.** Presented by Dr. M. R. Caro and (by invitation) Dr. J. M. Riddell.

**Nonthrombocytopenic Purpura, Henoch's Purpura, Acute Glomerulonephritis.** Presented by Dr. Malcolm C. Spencer.

**Case for Diagnosis: Disseminated Lupus Erythematosus? With Weber-Christian Disease?** Presented by Dr. Stephen Rothman and (by invitation) Dr. Richard B. Stoughton.

**Primary Systematized Amyloidosis with Macroglossia.** Presented by Dr. George C. Wells (by invitation).

## MANHATTAN DERMATOLOGIC SOCIETY

**Paul E. Bechet, M.D., *Co-President***

**Isadore Rosen, M.D., *Co-President***

**George M. Lewis, M.D., *Secretary***

***March 13, 1951***

**Localized Atopic Eczema (Commissures).** Presented by Dr. George M. Lewis.

F. K., a woman aged 36, noticed a small fissure in the left corner of the mouth five years ago. Two or three years ago the right corner fissured. Both fissures have been persistent, pruritic, and tender at times and limit the opening of the mouth. There has been some improvement in the summer, but recently the condition has become worse. She has been given two x-ray treatments, two radium treatments, and several courses of therapy with vitamins B and C, without effect.

Redness and superficial fissuring extend 3 mm. from both corners of the mouth. There is a thin, irregular, white film over the left buccal mucous membrane. The right mucous membrane shows some whiteness in lines adjacent to the biting edge.

A mycologic examination gave negative results.

Treatment was started with administration of antihistaminic drugs by mouth and application of zinc oxide paste without salicylic acid (Lassar's paste) locally. The condition has improved with this therapy.

DISCUSSION

Dr. Paul Gross: This case demonstrates how important it is to eliminate other possibilities before one speaks of vitamin deficiencies in conditions involving the lips and tongue. Perlèche due to riboflavin deficiency is comparatively rare. Most cases seen in our group of patients are due to infection with Candida albicans. Undoubtedly, the lichenification surrounding the angular fissures furnishes a clue to the diagnosis as presented by Dr. Lewis.

Dr. Perry Sachs: The patient frequently placed the rims of her glasses in her mouth. This habit might be worth investigating as a cause of a contact reaction.

Dr. George M. Lewis: This patient has not been given any instructions to change cosmetics. If any contact is operating now, it may be suppressed temporarily by the antihistamine; we will have to determine that later. Candida has apparently been eliminated as a cause because that organism is easy to culture from lesions of perlèche. The patient had received all sorts of vitamins, until, she said, they were running out her ears. She is now able to sleep. The antihistamines have at least contributed to symptomatic relief.

**Leprosy, Tuberculoid Type.** Presented by Dr. Orlando Canizares.

DISCUSSION

Dr. Orlando Canizares: We found this case interesting for several reasons. First, the patient was examined fairly recently in a hospital; a complete neurologic examination was done, but no diagnosis was made, although the changes in sensation were rather typical. There

were probably no cutaneous lesions at that time. Second, the tuberculoid type of leprosy doesn't respond well to therapy, but recently more than 50 patients have been treated with "sulphetrone" (4, 4'-bis[γ-phenyl-N-propylamino]-diphenylsulfone tetrasodium sulfonate) with fairly good results (Lowe, J.: The Sulfone Treatment of Tuberculoid Leprosy, *Internat. J. Leprosy* **18**:457 [Oct.-Dec.] 1950).

**Erythema Perstans.** Presented by DR. HERMAN SHARLIT.

R. W., a woman aged 46, complained of an eruption on both arms which had been present without interruption for 10 years. The past and family history was essentially unimportant, and there was no history of syphilitic infection. The patient has five children who are alive and well, and there were no miscarriages.

On both arms is a symmetrical eruption which consists of diffuse erythema, somewhat bluish in color, with ill-defined borders, not associated with subjective symptoms.

Routine laboratory examinations gave normal findings, except for the serologic examination, the results of which were reported as positive. On one occasion the following report of tests performed and their results was obtained:

| | |
|---|---|
| Mazzini test (undiluted) | 2 units |
| Kline exclusion test | 1 unit |
| Kolmer complement-fixation test | Negative |
| VDRL test | 3 units |
| Rein-Bossak cardiolipin test | 2 units |
| Cardiolipin complement-fixation test (undiluted; 3 units in dilution 1: 2) | 4 units |

On another occasion the following report of tests performed and their results was obtained:

| | |
|---|---|
| Mazzini test | 1 unit |
| VDRL test | 1 unit |
| Kline exclusion test | 1 unit |
| Rein-Bossak cardiolipin test | 1 unit |
| Kolmer complement-fixation test | 2 units |
| Cardiolipin complement-fixation test | 4 units |

A biopsy was reported as showing toxic erythema.

Four injections of a bismuth preparation did not change the appearance of the eruption.

DISCUSSION

DR. DAVID BLOOM: This case is impressive because of the extremely long duration of the erythema and the absence of any causative factor. The serologic report in this case may be disregarded. Such reports are frequently obtained nowadays because of the extreme sensitivity of the agents used in serologic diagnosis of syphilis.

DR. ANTHONY C. CIPOLLARO: Is this a progressive disease, or has it been *in statu quo?* [ANSWER: *In statu quo.*] Couldn't it be a nevus flammeus? May I ask that the diagnosis be given to this group at the next meeting?

DR. GEORGE M. LEWIS: Couldn't the history agree with a diagnosis of nevus tardus?

DR. MAURICE J. COSTELLO: I think this eruption is in some way related to light. It begins just about where her short sleeves end. It is possible that she had a severe sunburn and has had a persistent erythema. The eruption is also present on the cheek in a lighter form. I think telangiectasia is present there. On the posterior part of the arms there is infiltration of some of those lesions.

DR. PERRY SACHS: The slide shows an erythema multiforme type of reaction.

**Scleredema Adultorum (Buschke).** Presented by DR. GEORGE M. LEWIS.

J. D., an Italian woman aged 67, displayed redness, itching, and swelling of the face and forearms in June, 1950, after exposure to the sun. The condition was diagnosed as poison ivy dermatitis and treated with six poison ivy injections, following which there was increased swelling of the upper extremities and face, especially periorbitally. The process went on to vesiculation and bulla formation before resolving. In July, 1950, she came under the care of a dermatologist and stated that she received x-ray therapy to the face and upper extremities for several months.

Swelling and firmness of the skin of these parts have persisted with increase in pigmentation. On Jan. 31, 1951, the patient underwent cholecystectomy because of chronic cholecystitis with cholelithiasis and hydrops of the gall bladder. She also has hypertensive cardiovascular disease, hepatomegaly, and exogenous obesity.

There are diffuse hyperpigmentation and sclerosis of the skin over the face, neck, shoulders, and upper extremities. The subcutaneous tissues of the upper extremities are firm and unyielding to palpation, as are portions of the lower extremities, where pigmentation tends to be blotchy and slight. Joint mobility is not impaired. There is evidence of old varicose ulcers about both ankles.

Results of urinalysis were normal, and the Mazzini reaction of the blood was negative. The hemogram disclosed normal blood and differential counts. Blood chemical studies showed 7.2 gm. of total proteins, 4.4 gm. of albumin and 2.8 gm. of globulin. Cholesterol was 255 mg. and cholesterol esters 172 mg. per 100 cc., or 69.4%. The stool showed no parasites or ova, and the basal metabolic rate was + 8%.

A biopsy specimen from the right forearm taken in January, 1951, revealed pronounced hyperkeratosis with follicular plugging. The epidermis was normal; the granular layer was present, and pigmentation of the basal cells was greatly increased in some areas. Chromatophores were scattered throughout the midcutis, which showed vacuolation and homogenization of the collagen. The diagnosis was dermatitis actinica sequelae superimposed on scleroderma or possibly scleredema.

The patient had had recurrent episodes of dry, scaling dermatitis of the face, ears, and upper extremities and puffiness of the palpebrae for about 23 years, generally worse in the summertime. When she was seen in the Dermatology Clinic of the New York Hospital late in 1947 for this condition, an allergic background was suspected. There was acute urticarial reaction to sodium morrhuate injection for varicose veins.

There has been a spontaneous improvement of the condition of the skin during recent weeks.

DISCUSSION

DR. DAVID BLOOM: The patient shows pigmentation in addition to increased consistency of the skin, which makes me believe that the diagnosis is scleroderma rather than scleredema. The edema of the eyelids should make one consider the possibility of sclerodermatomyositis, although the patient does not complain of any muscular pain.

DR. WILBERT SACHS: The patient evidently has a mild radiodermatitis, which would account for a good part of the pigmentation. If so, it may end with some atrophy and then would look much more like dermatomyositis. The condition is scleredema adultorum and mild radiodermatitis.

DR. MAURICE J. COSTELLO: I agree with Dr. Bloom that this is the edematous stage of scleroderma. When the eruption undergoes involution, I believe you will see the true picture of scleroderma. At present, one cannot wrinkle the skin on the second or third phalanges. I believe pigmentation frequently is associated with scleroderma. I recall a patient sent to me who was thought to have Addison's disease, but who proved to have full-blown scleroderma. I believe this condition will prove to be that.

DR. ISADORE ROSEN: This patient gives a history of having had an acute infectious process with elevation in temperature some weeks prior to the development of the skin manifestations. This would speak in favor of the diagnosis of scleredema adultorum.

DR. GEORGE M. LEWIS: We anticipated a difference of opinion in this case if only because of one point; that is, it is difficult to see a patient once and know whether the process is retrograde or progressive. In this case there has been substantial improvement already, which I think would speak very much against scleroderma. The lesions as we see them are not distinctive.

**Sarcoidosis with Extensive Ulceration, Healed.** Presented by DR. ORLANDO CANIZARES.

J. H., a Negro man aged 35, is presented from the Bronx Veterans Administration Hospital. In 1945, while on duty in England, the patient exhibited lesions on the legs, which increased in size and number. He was returned to the United States for diagnosis and treatment. Biopsies of the skin of the legs and the lymph nodes confirmed the impression of sarcoidosis. At present, the patient complains of shortness of breath, nonproductive cough, and night sweats. Three

months ago he had denudation and ulceration of a few lesions on the legs, which have since healed with no specific therapy. Discrete, macular, slightly infiltrated, hyperpigmented lesions continue to develop.

There are many lesions scattered over the legs and thighs, with a few lesions on the forearms. The early lesion is a pigmented, slightly infiltrated macula. The larger, older lesions show slight central scarring and atrophy, with a tough, adherent scale and a peripheral, slightly elevated border. There are some lesions on the legs over the tibiae that show total denudation and ulceration. Two scars are visible, one in each groin below the inguinal ligament, where biopsy specimens of nodes were excised in 1946.

The tuberculin reaction was negative in second strength. Roentgenograms of the hands and feet showed no abnormality; that of the chest revealed reticular nodular infiltrate involving both lungs. The VRDL reaction was negative. The hemogram showed 5,410,000 red blood cells, 17.1 gm. of hemoglobin, and 6,700 white blood cells, with 59% polymorphonuclear leucocytes, 24% lymphocytes, 9% monocytes, and 2% eosinophiles. The blood calcium was 9.9 gm., phosphorus 3.4 gm., and total proteins 7.8 gm., with 3.6 gm. of albumin and 4.2 gm. of globulin.

A biopsy specimen of the skin was diagnosed as showing sarcoidosis.

DISCUSSION

DR. WILBERT SACHS: The slide shows a typical sarcoid picture.

DR. DAVID BLOOM: The eruption has an unusual distribution in this patient, involving only the lower extremities. It belongs to the group of cases which are called sarcoidosis in Negroes and which I prefer to term, as Nomland did, hematogenous cutaneous tuberculosis in the Negro.

DR. ANTHONY C. CIPOLLARO: There is no question that histologically this condition is absolutely typical of the superficial Boeck type of sarcoid, but I must remark that in either the Negro or in the white race one rarely sees these deep scars resulting from sarcoid without its going through the stage of ulceration. If the history is correct in that all these scarred areas did not ulcerate, it is one of the rarest things to occur in sarcoidosis. Occasionally in the Darier-Roussy type of sarcoid one will find ulcers. I thought of some such condition as Bazin's disease (tuberculosis indurativa [erythema induratum]) or an unusually extensive type of necrotic tuberculid, not the papular but the nodular type.

DR. MAURICE J. COSTELLO: A few years ago we had a series of unusual cases of sarcoid at Bellevue Hospital, with ulcers of the tips of the fingers, foreshortening of the fingers, spontaneous amputations, osteomyelitis, etc.

DR. ORLANDO CANIZARES: I agree with Dr. Costello. In some cases it is difficult to differentiate between sarcoid and leprosy. In this case we looked for leprosy, but all examinations have given negative results. The fact that the patient has some changes in the lungs and an inverted albumin-globulin ratio, I think, points more to a diagnosis of sarcoid.

**Keratosis Follicularis Benefited by Vitamin A Therapy.** Presented by DR. GEORGE M. LEWIS.
**Case for Diagnosis: Lichen Planus? Pityriasis Rosea?** Presented by DR. GEORGE M. LEWIS.
**Lupus Miliaris Faciei.** Presented by DR. DAVID BLOOM.
**Osteoma at Tip of Finger.** Presented by DR. DAVID BLOOM.
**Actinomycosis.** Presented by DR. ORLANDO CANIZARES.

# News and Comment

## ANNOUNCEMENTS

**Affiliation Between the Skin and Cancer Hospital of Philadelphia and the Graduate School of Medicine of the University of Pennsylvania.**—Dr. Bertram Shaffer, Medical Director of The Skin and Cancer Hospital of Philadelphia, has announced the establishment of a medical affiliation between the Skin and Cancer Hospital and the Graduate School of Medicine of the University of Pennsylvania.

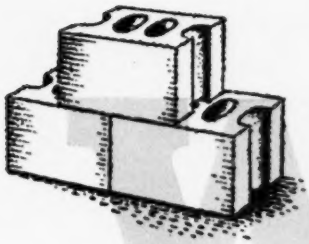
The Skin and Cancer Hospital will retain its corporative identity, but the Graduate School of Medicine has agreed to be responsible for the professional and educational standards of the institution.

A new Medical Board has been created which will act also as the Executive Committee of the Medical Staff. This consists of six chiefs of service with the title of Attending Dermatologists, namely: Dr. Donald M. Pillsbury, Dr. Carroll S. Wright, Dr. H. E. Twining, Dr. Reuben Friedman, Dr. H. M. Samitz, and Dr. Edward Ozellers. The Medical Board includes also Dr. Herman Beerman, Chairman of the Department of Dermatology and Syphilology, Graduate School of Medicine, and Dr. Bertram Shaffer, Medical Director. Dr. Pillsbury will be the Chairman of the Medical Board.

Under this new arrangement, the hospital will be staffed by dermatologists from institutions throughout the city, and it will participate in graduate teaching in dermatology of residents and fellows associated with these institutions.

## CORRECTION

In the article by Dr. Flesch and Dr. Hunt entitled "Local Depilatory Action of Some Unsaturated Compounds," published in the March, 1952, issue of the A. M. A. ARCHIVES, page 261, the legend now under Figure 5 belongs under Figure 6 and that under Figure 6 belongs under Figure 5.



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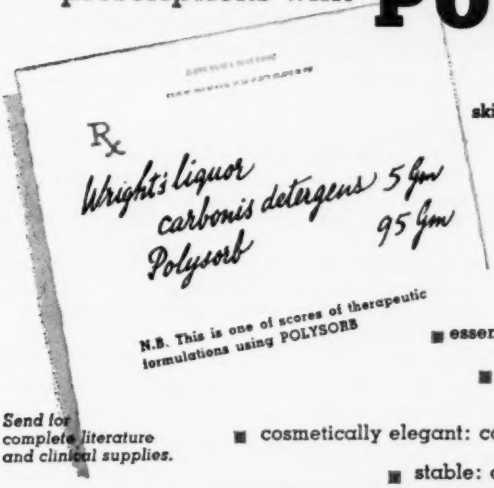
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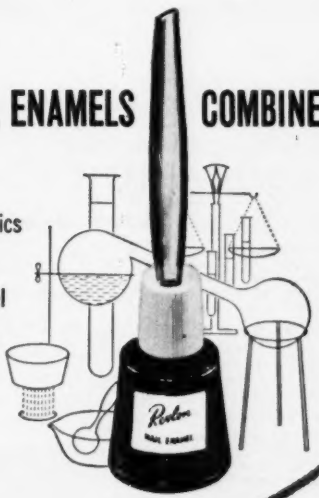


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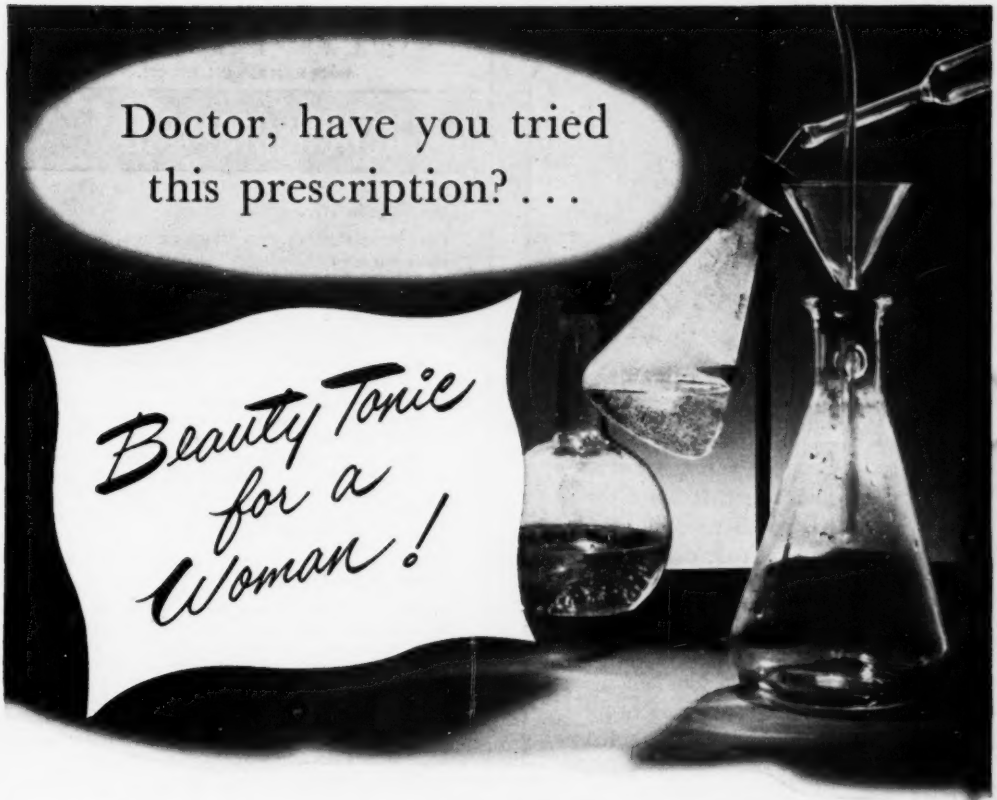


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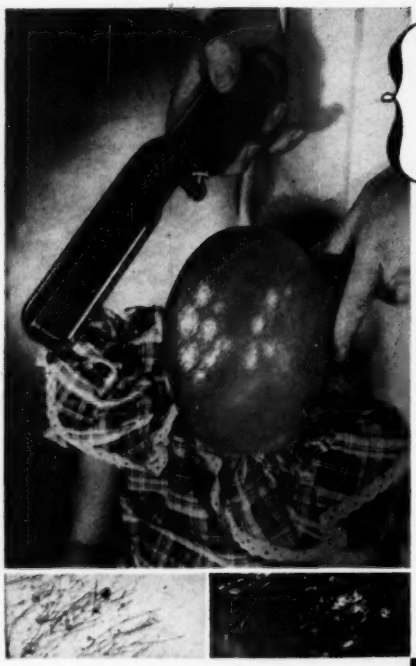

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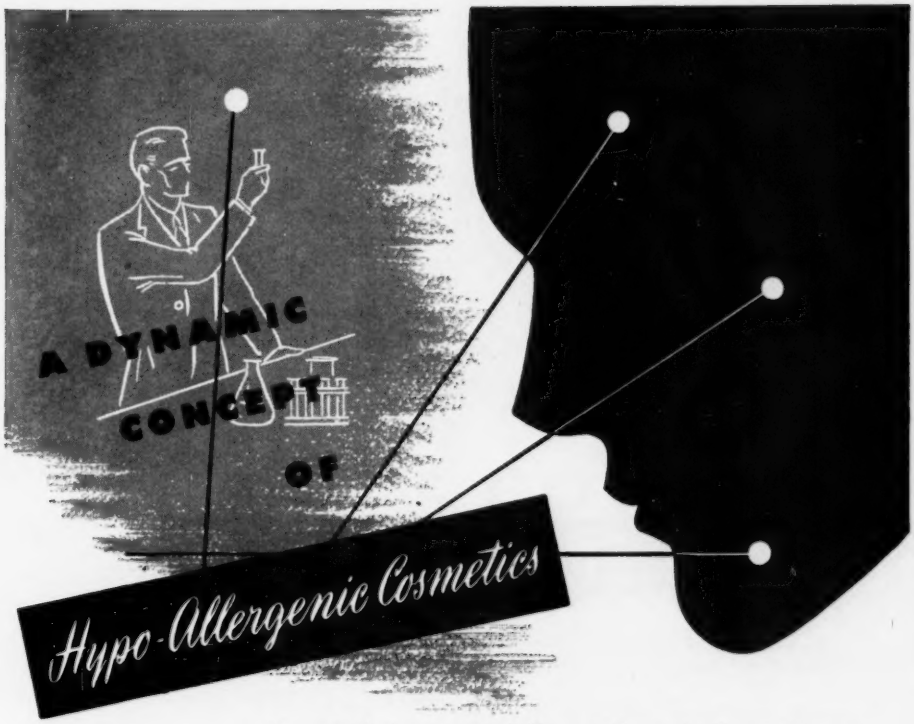


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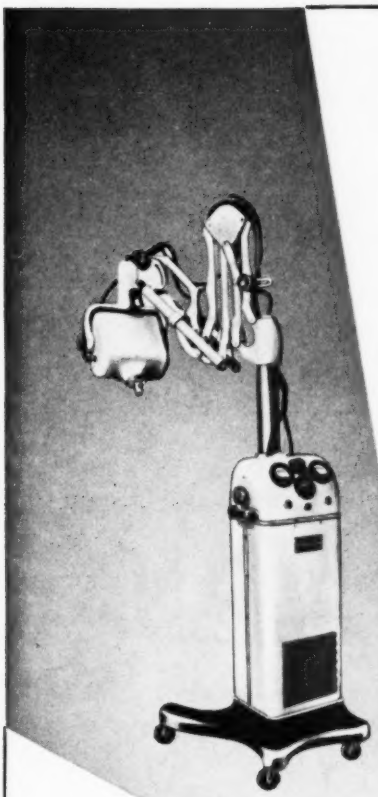
***References:***

1. Rothman, J. and Shapiro, A. L.: Med. Clin. N. Amer. 33:274-5, Jan., 1949.
2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.



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